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SYNTHALIN

ITS USE IN THE TREATMENT OF DIABETES *

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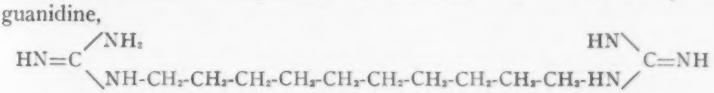
Since the introduction of insulin in the treatment of patients with diabetes, various investigations have been conducted to find a remedy which would exert an influence on diabetes similar to that of insulin, but which could be administered orally.

During the course of the last year, a synthetic compound named "synthalin" was developed by Frank [1] in Minkowski's clinic [2] in Breslau. The exact chemical composition of this substance is deca-methyl-diguanidine,



In their first communication, these authors report that they were able to reduce the blood sugar concentration in completely depancreatized dogs and rabbits by administering synthalin either subcutaneously or orally. In these animals the blood dextrose dropped from 314 mg. per hundred cubic centimeters of blood to 70, and from 426 to 90. The clinical symptoms of hypoglycemia, convulsions and general paralysis, from which the animals recovered on the administration of dextrose, accompanied this drop in the blood sugar.

In their studies on diabetic patients who excreted as much as 40 Gm. of dextrose a day, they report a marked drop or the disappearance of

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1. Frank, E.; Nothmann, M., and Wagner, A.: Ueber synthetisch dargestellte Körper mit insulinartiger Wirkung auf den normalen und diabetischen Organismus, Klin. Wchnschr. **5**:2100, 1926; Die Synthalinbehandlung des Diabetes mellitus, Deutsche. med. Wchnschr. **52**:2067, 1926; ibid. **52**:2107, 1926.

2. Minkowski, O.: Synthetische insulinähnlich wirkende Substanzen, Klin. Wchnschr. **5**:2107, 1926.

the urinary sugar; ketone bodies also disappeared from the urine. The blood dextrose concentration came down to normal, and the patients were able to gain in body weight, though not as dramatically as after the administration of insulin.

They administer the drug in doses of from 20 to 25 mg. twice a day on the first and third days, one dose on the second and omit it entirely on the fourth day. The reason for this procedure is that frequently after-effects develop which are due to an overdose of the synthalin. The usual symptoms caused by an overdose of synthalin are anorexia, pressure in the epigastrium, nausea and vomiting and in more severe cases, diarrhea.

In January, 1927, H. A. Metz, supplied us with synthalin that he had obtained from the Kahlbaum Company. We immediately began the studies subsequently reported.

For this study, we selected patients with diabetes of different grades of severity and those who gave the greatest promise of complete cooperation.

REPORT OF CASES

CASE 1.—E. J., a girl, aged 13, had had poliomyelitis in 1918, measles in 1920, scarlet fever in 1922, chickenpox and whooping cough in 1923. In March, 1926, the patient began to have polyuria, nocturia, pruritus vulvae and loss in weight; these symptoms led to a urinary examination and to the discovery of diabetes. The patient's weight at that time was 73 pounds (33.1 Kg.); the blood pressure was 120 systolic and 70 diastolic; the heart, lungs and abdomen were normal. When first examined, the urine showed a specific gravity of 1.028; dextrose, 3 per cent; albumin was not present; there was some acetone and diacetic acid. The blood sugar concentration during fasting was 195 mg. per hundred cubic centimeters; the carbon dioxide capacity of the blood was 53 per cent by volume. The patient was placed on a diet consisting of 40 Gm. of carbohydrate, 75 Gm. of protein and 100 Gm. of fat, total calories 1,360, and 18 units of insulin twice a day. On this regimen, the urine became free from sugar and ketone bodies, and the fasting blood sugar came down to 133 mg. per hundred cubic centimeters.

By June, 1926, the general condition of the patient improved materially. Her weight increased to 79½ pounds (36 Kg.). Her diet was increased to 75 Gm. of carbohydrate, 75 Gm. of protein and 150 Gm. of fat. Twelve units of insulin were administered once a day. The blood sugar concentration was 133, 117 and 148 on three different examinations. On July 9, the injections of insulin were stopped. On July 29, the urinary sugar was 2 per cent; there were no ketones, and the blood sugar was 182. The injections of insulin were resumed, 14 units once a day being given. On August 25, the blood sugar was 128; and sugar was not present in the urine; on November 20, the blood sugar was 154 mg. per hundred cubic centimeters, and on December 24 the blood sugar was 102. Urinary sugar was not found.

Our plan of procedure in testing the efficacy of synthalin was to stop the injections of insulin for a short period of time in order to determine the patient's ability to burn dextrose without the help of the hormone and then to substitute synthalin for the insulin.

The results of our study are tabulated in table 1. For the sake of convenience, each separate study is divided into periods. The patient's food was weighed carefully; the urine collected quantitatively and analyzed daily. The patient's weight was taken weekly, and the blood was examined at frequent intervals. Throughout the entire study, the patient was given 75 Gm. of carbohydrate, 75 Gm. of protein and 150 Gm. of fat; she had been kept on this diet for months previous to the present study.

On January 12, the patient was given the last dose of insulin. During the first period (from January 13 to 15) insulin was not given. It is noticeable from the chart that glycosuria promptly developed, becoming more marked with each day.

During the second period (January 16 to 25) synthalin was administered as follows: two 10 mg. tablets on the first day, one tablet on the second day and again two tablets on the third and fourth days, after which there was an interruption. On January 20, the patient developed epigastric distress, nausea and anorexia. By January 24, she could consume only two thirds of her diet, and even that had to be forced. The sugar in the urine cleared up, but it was difficult to decide whether the synthalin was responsible or whether this occurred because the patient had taken less food. During the third period, the feeding of synthalin was interrupted until the gastric symptoms subsided.

On January 31, the patient's condition improved so that she was able to partake of her full diet (fourth period). She developed glycosuria during those four days on full diet without synthalin. By the fourth day, she excreted as much as 31 Gm. of dextrose. Her weight then was 75 pounds (34 Kg.), a loss of 3½ pounds (1.6 Kg.) since the beginning of our study.

From February 4 to 20 (the fifth period), the patient was kept on synthalin and was given the full diet. The glycosuria was promptly reduced, and the gastric distress was not so marked as during the second period. She was able to partake of all her food except during one day. In spite of this, however, her body weight came down to 74 pounds (33.6 Kg.), and on February 12, the blood sugar was 210 mg. per hundred cubic centimeters. During the last three days of this period, she was practically sugar-free.

During the sixth period (from February 21 to 27), the synthalin was withdrawn and glycosuria promptly recurred. On February 24, ketonuria developed. On the last day of this period (February 27), the excretion of dextrose reached 25 Gm., and there was 2 Gm. of acetone bodies a day. During the seventh period (from February 28 to March 11), synthalin was administered again. Glycosuria and ketonuria gradually disappeared, and the blood sugar on the last day was 138 mg. There was no further loss of body weight. Gastric distress persisted during the period at irregular intervals, but not enough to interfere with the patient's ability to consume all of her food.

During the eighth period (from March 12 to 20), the synthalin was withdrawn again. Glycosuria and ketonuria promptly reappeared, gradually increasing, so that on the last day of this period, the patient excreted as much as 1.5 Gm. of ketone bodies and 31 Gm. of dextrose.

During the ninth period (from March 21 to May 13), synthalin was given as indicated in table 1, every third dose being omitted. With the exception of occasional gastric distress, the patient felt well most of the time. She was able to partake of her full diet and gained in weight to 76 pounds (34.5 Kg.). The urinary sugar and ketone bodies cleared up within about one week, the former reappearing on but a few occasions.

TABLE 1.—*Results of Study in Case 1*

Period	Date	Urine					Diet			Blood Sugar	Body Weight, Pounds	Insulin, Units		Synthalin, Mg.		Remarks
		Volume, Cc.	Specific Gravity	Dextrose, Gm.	Acetone and Diacetic, Gm.	Nitrogen, Gm.	Carbohydrate	Protein	Fat			A. M.	P. M.	A. M.	P. M.	
	12/24/26	.....	.....	..	....	....	75	75	150	102	..	12				
I	1/13/27	840	1.024	2	—*	....	75	71	150							
	1/14/27	1,100	1.015	6	—	....	75	75	150							
	1/15/27	1,500	.....	7	—	....	75	75	121	167	78½					
II	1/16/27	1,080	1.024	14	—	....	75	64	149	...	..	..	..	10	10	
	1/17/27	1,000	1.020	10	—	....	74	75	151	...	..	..	..	10	—	
	1/18/27	850	1.032	15	—	....	74	75	150	...	..	..	..	10	10	
	1/19/27	1,000	1.015	3	—	....	70	58	74	...	..	..	..	10	10	
	1/20/27	960	1.020	4	—	....	75	45	64	...	..	..	..	—	—	Nausea; gastric distress
	1/21/27	960	1.020	2	—	....	52	44	68	...	..	..	..	25	—	Nausea; gastric distress
	1/22/27	832	1.015	1	—	....	62	72	73	...	..	..	..	25	—	Nausea; gastric distress
	1/23/27	800	1.016	0	—	....	54	63	103	...	..	..	..	25	25	Anorexia
	1/24/27	.....	.....	0	—	....	65	62	94	...	..	..	..	25	25	Gastric distress
	1/25/27	.....	.....	0	—	....	65	60	78	...	..	..	..	25	—	Gastric distress
III	1/26/27	900	1.015	0	—	....	65	75	128	...	..	..	..	...	....	Feels better
	1/27/27	1,600	1.015	0	—	....	67	71	61							
	1/28/27	1,700	1.012	3	—	....	75	72	116							
	1/29/27	1,200	1.012	4	—	....	75	71	145							
	1/30/27	1,250	1.017	10	—	....	76	54	79	...	..	..	..	....	...	Anorexia; feels well
IV	1/31/27	1,000	1.020	10	—	....	75	75	150							
	2/ 1/27	1,000	1.020	14	—	....	75	75	150							
	2/ 2/27	950	1.027	17	—	....	75	75	150							
	2/ 3/27	1,200	1.034	31	—	....	75	75	150	...	75					
V	2/ 4/27	960	1.015	0	—	...	74	75	150	...	..	..	..	25	25	Vomited dinner
	2/ 5/27	900	1.020	8	—	....	75	75	150	...	..	..	..	—	—	
	2/ 6/27	480	1.018	0	—	....	76	75	151	...	..	..	..	25	12.5	Vomited dinner
	2/ 7/27	990	1.017	11	—	....	64	51	139	...	..	..	..	—	—	Nausea; anorexia
	2/ 8/27	1,350	1.013	8	—	....	75	75	149	...	..	..	..	12.5	12.5	Nausea
	2/ 9/27	930	1.015	6	—	....	75	75	132	...	..	..	..	12.5	—	
	2/10/27	1,000	1.014	±	—	....	75	75	141	...	..	..	..	12.5	12.5	Feels well
	2/11/27	960	1.017	3	—	....	75	76	150	...	..	..	..	12.5	—	

	2/12/27	960	1.015	0	—	....	75	75	150	210	..	..	..	12.5	12.5	
	2/13/27	1,170	1.020	4	—	....	75	75	150	...	..	..	..	12.5	12.5	
	2/14/27	1,000	1.022	11	—	....	75	75	150	...	..	..	..	—	—	
	2/15/27	930	1.016	9	—	....	75	76	151	...	..	..	..	12.5	12.5	
	2/16/27	1,000	1.017	2	—	....	75	75	125	...	..	..	..	12.5	—	
	2/17/27	865	1.015	2	—	....	75	75	150	...	..	..	..	12.5	12.5	
	2/18/27	930	1.018	0	—	....	75	75	150	...	74	..	..	12.5	12.5	Gastric distress in p. m.
	2/19/27	1,000	1.017	0	—	....	75	75	116	...	..	..	..	12.5	12.5	
	2/20/27	960	1.017	2	—	....	76	75	150	...	..	..	..	12.5	12.5	Gastric distress
VI	2/21/27	1,200	1.018	6	—	....	75	75	133							
	2/22/27	1,000	1.018	10	—	....	75	75	131							
	2/23/27	1,030	1.022	21	—	....	75	75	130							
	2/24/27	1,200	1.017	20	+	....	75	75	149							
	2/25/27	1,090	1.024	21	+	....	75	76	150							
	2/26/27	1,220	1.025	22	1.06	....	75	75	150							
	2/27/27	1,130	1.028	25	2.00	....	75	66	132							
VII	2/28/27	930	1.028	19	1.06	....	75	75	150	...	..	..	..	12.5	12.5	
	3/ 1/27	770	1.026	15	0.92	....	75	75	150	...	..	..	..	12.5	12.5	
	3/ 2/27	980	1.022	14	0.45	....	74	69	130	...	..	..	..	12.5	—	Gastric distress; refused supper
	3/ 3/27	900	1.017	11	0.33	....	75	75	150	...	..	..	..	12.5	12.5	
	3/ 4/27	770	1.015	7	0.38	....	75	75	150	...	..	..	..	12.5	12.5	Feels well
	3/ 5/27	930	1.018	5	0.29	10.2	75	75	149	...	..	..	..	12.5	12.5	
	3/ 6/27	1,210	1.022	10	0.29	10.2	74	60	130	...	..	..	..	12.5	—	Gastric distress; anorexia
	3/ 7/27	1,000	1.020	5	0.42	9.6	75	54	118	...	..	..	..	12.5	—	Feels better
	3/ 8/27	1,000	1.021	5	—	....	75	75	120	...	..	..	..	12.5	12.5	
	3/ 9/27	930	1.022	0	—	....	75	75	149	...	..	..	..	12.5	12.5	
	3/10/27	900	1.014	0	—	....	76	75	149	...	..	..	..	12.5	12.5	Vomited, midnight
	3/11/27	1,030	1.015	0	—	....	75	75	150	138	..	..	..	12.5	—	Gastric distress; nausea; diarrhea
VIII	3/12/27	1,000	1.013	2	0.21	....	75	74	101	...	74½	..	..	....	....	Anorexia
	3/13/27	1,060	1.017	4	0.71	11.2	75	62	150							
	3/14/27	1,000	1.020	10	0.73	10.6	75	65	150							
	3/15/27	1,000	1.022	16	0.80	....	75	75	150							
	3/16/27	1,000	1.015	21	0.49	....	75	75	150							
	3/17/27	960	1.020	19	0.83	12.0	75	75	150							
	3/18/27	1,150	1.022	19	....	12.0	75	75	113							
	3/19/27	1,192	1.026	24	0.96	11.7	75	75	124							
	3/20/27	1,256	1.025	31	1.57	13.3	75	60	122	...	74					
IX	3/21/27	1,192	1.020	27	0.83	10.2	75	75	150	..	..	..	..	12.5	12.5	
	3/22/27	865	1.020	7	0.33	9.6	75	75	150	...	..	..	..	12.5	12.5	
	3/23/27	1,192	1.015	5	0.20	9.8	75	75	150	...	..	..	..	—	12.5	
	3/24/27	990	1.012	4	0.15	8.3	75	75	150	...	..	..	..	12.5	12.5	
	3/25/27	1,450	1.020	5	0.17	9.7	75	75	117	...	..	..	..	12.5	—	Nausea slight
	3/26/27	1,032	1.015	2	0.18	8.6	75	75	103	...	..	..	..	12.5	12.5	Gastric distress

* — signifies acetone absent by qualitative test; + signifies acetone present by qualitative test.

TABLE 1.—*Results of Study in Case 1—Continued*

Period	Date	Urine					Diet			Blood Sugar	Body Weight, Pounds	Insulin, Units		Synthalin, Mg.		Remarks
		Volume, Cc.	Specific Gravity	Dextrose, Gm.	Acetone and Diacetic, Gm.	Nitrogen, Gm.	Carbohydrate	Protein	Fat			A. M.	P. M.	A. M.	P. M.	
IX (cont.)	3/27/27	1,032	1.017	3	—	9.6	75	66	136	...	..	..	..	12.5	12.5	Diarrhea
	3/28/27	1,030	1.015	3	—	8.7	75	76	150	...	..	..	..	—	12.5	
	3/29/27	1,000	1.015	5	—	8.8	75	66	144	...	..	..	..	12.5	—	
	3/30/27	1,000	1.012	3	—	8.5	76	75	150	...	..	..	..	—	12.5	
	3/31/27	1,000	1.014	3	—	8.8	75	75	150	...	..	..	..	12.5	12.5	
	4/ 1/27	1,190	1.014	0	—	....	75	75	112	...	..	..	..	—	12.5	
	4/ 2/27	930	1.015	0	—	....	74	74	95	...	74½	..	..	12.5	12.5	Anorexia
	4/ 3/27	1,000	1.014	0	—	....	75	58	128	...	..	..	..	—	12.5	
	4/ 4/27	1,000	1.014	0	—	....	76	61	125	...	..	..	..	12.5	12.5	
	4/ 5/27	1,000	1.014	0	—	....	75	75	133	...	..	..	..	—	12.5	Gastric distress
	4/ 6/27	1,000	1.015	0	—	....	75	75	137	...	..	..	..	12.5	12.5	
	4/ 7/27	1,000	1.016	0	—	....	75	76	150	...	..	..	..	—	12.5	
	4/ 8/27	.....	.....	..	....	....	..	..	...	...	..	..	..	12.5	12.5	Nausea; diarrhea
	4/ 9/27	1,000	1.012	0	—	....	75	75	94	153	..	..	..	—	12.5	Nausea
	4/10/27	1,000	1.015	0	—	....	75	58	123	...	..	..	..	—	12.5	Feels well
	4/11/27	1,032	1.015	0	—	....	75	75	150	...	..	..	..	—	12.5	
	4/12/27	1,120	1.014	4	—	....	75	75	150	...	..	..	..	—	12.5	
	4/13/27	1,000	1.017	5	—	....	76	75	149	...	..	..	..	—	12.5	
	4/14/27	1,000	1.017	5	—	....	76	75	118	...	..	..	..	—	12.5	
	4/15/27	1,000	1.015	0	—	....	75	75	132	...	..	..	..	12.5	—	
	4/16/27	1,032	1.012	0	—	....	75	75	122	...	..	..	..	12.5	12.5	
	4/17/27	1,120	1.016	0	—	....	75	65	128	...	..	..	..	—	12.5	
	4/18/27	1,320	1.016	5	—	....	75	75	150	...	..	..	..	12.5	—	
	4/19/27	1,064	1.015	4	—	....	75	75	144	...	..	..	..	12.5	12.5	
	4/20/27	920	1.012	2	—	....	75	75	150	...	..	..	..	—	12.5	
	4/21/27	1,000	1.012	0	—	....	75	75	150	...	..	..	..	12.5	—	
	4/22/27	1,000	1.014	0	—	....	75	75	113	...	..	..	..	12.5	12.5	
	4/23/27	1,210	1.014	0	—	....	75	75	119	...	..	..	..	—	12.5	
	4/24/27	1,120	1.017	0	—	....	75	76	126	...	..	..	..	12.5	—	
	4/25/27	1,064	1.015	0	—	....	75	75	150	...	..	..	..	12.5	12.5	
	4/26/27	.....	.....	..	....	....	..	..	...	...	..	..	..	—	12.5	
	4/27/27	1,032	1.012	0	—	....	75	75	150	...	..	..	..	12.5	—	
	4/28/27	1,032	1.012	0	—	....	76	76	150	...	..	..	..	12.5	12.5	
	4/29/27	1,030	1.012	0	—	....	75	75	123	...	..	..	..	—	12.5	
	4/30/27	1,030	1.012	0	—	....	76	73	127	...	..	..	..	12.5	—	
	5/ 1/27	1,050	1.016	+	—	....	75	75	150	...	..	..	..	12.5	12.5	

	5/ 2/27	1,110	1.017	++	—	....	75	73	130	...	..	..	..	—	12.5	
	5/ 3/27	1,110	1.016	++	—	....	75	75	149	...	..	..	..	12.5	—	
	5/ 4/27	1,000	1.015	4	—	....	75	75	150	...	..	..	..	12.5	12.5	
	5/ 5/27	960	1.015	4	—	....	76	76	150	...	..	..	..	—	12.5	
	5/ 6/27	1,062	1.012	0	—	....	76	75	150	...	76	..	..	12.5	—	
	5/ 7/27	1,000	1.014	0	—	....	75	75	124	...	..	..	..	12.5	12.5	
	5/ 8/27	1,080	1.015	0	—	....	75	67	150	...	..	..	..	—	12.5	
	5/ 9/27	1,000	1.015	3	—	....	75	75	150	...	..	..	..	12.5	—	
	5/10/27	960	1.012	0	—	....	75	75	150	...	..	..	..	12.5	12.5	
	5/11/27	1,000	1.012	3	—	....	75	75	150	...	..	..	..	—	12.5	
	5/12/27	1,030	1.012	0	—	....	75	75	150	...	..	..	..	12.5	—	
	5/13/27	1,000	1.013	0	—	....	75	75	125	...	..	..	..	12.5	12.5	
X	5/14/27	960	1.014	0	—	....	75	69	143	180	..	10				
	5/15/27	1,180	1.015	0	—	....	75	67	150	...	..	10				
	5/16/27	1,240	1.016	4	—	....	75	75	150	...	..	10				
	5/17/27	1,120	1.016	3	—	....	75	75	150	...	..	10				
	5/18/27	1,000	1.017	6	—	....	75	75	150	...	..	10				
	5/19/27	960	1.017	6	—	....	75	75	150	...	..	10				
	5/20/27	960	1.017	5	—	....	75	75	150	...	77½	10				
	5/21/27	1,100	1.014	++	—	....	75	75	150	...	..	14				
	5/22/27	1,120	1.016	0	—	....	75	70	139	...	..	14				
	5/23/27	960	1.018	5	—	....	75	74	150	...	..	14				
	5/24/27	1,000	1.018	6	—	....	75	75	150	...	..	14				
	5/25/27	1,000	1.018	9	—	....	77	84	150	...	..	14				
	5/26/27	1,060	1.020	10	—	....	75	75	150	...	..	14				
	5/27/27	925	1.020	4	—	....	75	75	150	...	..	14				
XI	5/28/27	1,000	1.020	8	—	....	76	75	150	...	78	..	..	—	12.5	
	5/29/27	930	1.024	9	—	....	75	75	150	...	..	..	..	12.5	—	Nausea; diarrhea
	5/30/27	1,160	1.015	7	—	....	75	75	150	...	..	..	..	12.5	12.5	
	5/31/27	1,130	1.015	8	—	....	75	75	150	...	..	..	..	—	12.5	
	6/ 1/27	800	1.022	4	—	....	72	73	150	...	..	..	..	12.5	12.5	Nausea; vomited after p. m. synthalin
	6/ 2/27	980	1.014	0	—	....	75	75	150	...	..	..	..	—	12.5	
	6/ 3/27	870	1.015	0	—	....	75	75	150	...	..	..	..	12.5	—	
	6/ 4/27	800	1.016	0	—	....	75	75	150	...	78	..	..	12.5	12.5	
	6/ 5/27	1,090	1.018	0	—	....	75	73	149	...	..	..	..	—	12.5	
	6/ 6/27	1,100	1.015	0	—	....	75	58	131	...	..	..	..	12.5	—	
	6/ 7/27	1,000	1.012	++	—	....	75	74	150	...	..	..	..	12.5	12.5	
	6/ 8/27	930	1.015	++	—	....	75	74	150	...	..	..	..	—	12.5	
	6/ 9/27	1,120	1.012	++	—	....	75	75	150	...	..	..	..	12.5	—	
	6/10/27	930	1.015	0	—	....	75	75	149	...	..	..	..	12.5	12.5	
	6/11/27	930	1.015	0	—	....	75	75	150	365	77½	..	..	—	12.5	
	6/12/27	1,030	1.014	0	—	....	75	75	150	...	..	..	..	12.5	—	
	6/13/27	1,150	1.017	0	—	....	75	69	141	...	..	..	..	12.5	12.5	
	6/27/27	1,000	1.014	0	—	....	75	75	150	...	78¾	..	..	12.5	12.5	
	7/ 7/27	1,030	1.012	0	—	....	75	75	150	...	..	..	..	12.5	12.5	

During the tenth period (from May 14 to 27), synthalin was withdrawn and insulin was substituted. The reason for that experiment was to determine whether any change in tolerance had occurred during the past five months that the patient had not been given insulin. We found that doses of insulin that could keep her aglycosuric then could not do it after the period during which insulin had not been administered. Raising of the dosage of insulin to 14 units did not clear up the condition, indicating that probably the tendency of the patient's natural tolerance was downward.

From May 28 to the time this article was written (the eleventh period) the patient was receiving synthalin in 12.5 mg. doses, every third dose being omitted. On this schedule she has but occasional attacks of gastric distress, and these are slight. She remains free from sugar and ketones. The last time she was examined her blood sugar was 165 mg. per hundred cubic centimeters, and her body weight was 77¼ pounds (35 Kg.).

CASE 2.—J. L., a girl, aged 13, was admitted to the hospital on Oct. 14, 1923, complaining of weakness, polyphagia and polydypsia of eight months' duration. Her weight was 73 pounds (33.1 Kg.) and her fasting blood sugar, 320 mg. On a diet consisting of 25 Gm. of carbohydrate, 75 Gm. of protein and 100 Gm. of fat and 8 units of insulin twice a day, her urine was sugar-free and acetone-free, whereas without insulin she excreted from 25 to 30 Gm. of dextrose and from 4 to 6 Gm. of acetone bodies a day. She was discharged from the hospital on June 29, 1924, weighing 91 pounds (41.3 Kg.) and feeling much improved.

On Nov. 14, 1924, following a cold of about one week's duration, she was readmitted in impending diabetic coma. Her blood sugar was 335 mg. per hundred centimeters of blood and carbon dioxide combining power, 21.2 per cent by volume. The urine contained large amounts of dextrose and acetone and a faint trace of albumin. The results of physical examination were negative except that drowsiness, Kussmaul breathing, a rapid pulse rate (120 per minute) and temperature ranging between 100 to 102 F. were noted. Two days later, she was entirely free from symptoms and felt well. During this period at the hospital, the patient excreted from 10 to 15 Gm. of dextrose a day on a diet of 35 Gm. of carbohydrate, 75 Gm. of protein, and 125 Gm. of fat and the administration of 20 units of insulin twice a day. She was discharged September 5, improved, although her carbohydrate tolerance was less than during her first stay at the hospital.

On Jan. 5, 1927, the patient was readmitted in impending diabetic coma. She gave a history of general malaise for a few weeks prior to January 5, when she began to vomit, became dyspneic and drowsy; she was therefore brought to the hospital.

Physical examination revealed signs of impending diabetic coma, drowsiness, Kussmaul breathing, rapid pulse rate (140 per minute), cold extremities and a temperature of 99.2 F. Urinalysis showed the presence of large amounts of dextrose and acetone. The patient was treated with insulin, alkali, carbohydrate and forced fluids, and the next morning she was feeling better.

Throughout January, February and March, she was kept on 50 Gm. of carbohydrate, 75 Gm. of protein and 125 Gm. of fat, and 20 units of insulin was administered twice a day. On this regimen she excreted both dextrose and ketone bodies. She therefore offered us an excellent opportunity to study the influence of synthalin on glycosuria and ketoses unaided by insulin. On January 17, she received two doses of 25 mg. of synthalin and two doses of insulin of 30 and 15 units. On that day, she excreted 53 Gm. of dextrose and

TABLE 2.—*Results of Study in Case 2*

Period	Date	Urine				Diet			Body Weight, Pounds	Insulin, Units		Synthalin, Mg.		Remarks
		Volume, Cc.	Specific Gravity	Dextrose, Gm.	Acetone Bodies, Gm.	Carbohydrate	Protein	Fat		A. M.	P. M.	A. M.	P. M.	
I	3/ 4/27	1,350	1.022	18	2.02	51	75	125	...	20	20	25	25	
	3/ 5/27	1,620	1.017	24	2.16	50	74	126	...	20	20	25	25	
	3/ 6/27	1,220	1.015	12	1.48	50	74	126	...	20	20	—	—	
	3/ 7/27	1,400	1.021	25	2.49	51	74	126	...	20	20	25	25	
	3/ 8/27	1,630	1.021	29	3.01	50	75	125	105	20	20	25	25	
	3/ 9/27	1,690	1.018	24	2.07	50	74	125	...	20	20	35	35	
	3/10/27	1,620	1.016	17	1.34	51	75	124	...	20	20	35	—	Vertigo at noon
	3/11/27	1,520	1.015	14	1.00	50	75	125	...	20	20	35	35	
	3/12/27	1,560	1.017	20	0.79	50	76	124	...	20	20	35	35	
	3/13/27	1,680	1.014	11	0.65	51	75	125	...	20	20	35	—	Vomited breakfast
	3/14/27	1,600	1.011	8	0.75	49	75	125	...	20	20	—	—	
	3/15/27	1,450	1.021	39	1.99	51	74	126	103	20	20	25	30	
	3/16/27	1,270	1.021	21	1.40	45	74	125	...	20	20	30	30	Vomiting
Average per day				20										
II	3/17/27	1,000	1.019	20	0.71	51	74	126	...	20	20			
	3/18/27	1,330	1.019	36	0.62	51	75	125	...	20	20			
	3/19/27	1,560	1.024	44	1.61	50	74	126	...	20	20			
	3/20/27	1,400	1.021	33	1.46	50	75	125	...	20	20			
	3/21/27	1,280	1.024	40	2.40	51	74	126	...	20	20			
	3/22/27	1,370	1.025	43	3.65	50	75	125	102	20	20			
Average per day				36										
III	3/23/27	1,630	1.023	56	1.98	50	75	125	...	20	20	—	35	
	3/24/27	1,530	1.025	39	2.81	51	75	124	...	20	20	25	20	
	3/25/27	1,480	1.022	37	0.94	50	75	125	103	20	20	30	30	Vertigo in afternoon
	3/26/27	1,230	1.016	9	0.44	50	76	124	...	20	20	30	30	

2.34 Gm. of acetone bodies in the urine. On January, 18, she received only 30 units of insulin and 25 mg. of synthalin twice a day. On January 19, she received synthalin in two 25 mg. doses but no insulin in the morning. On that day, she excreted 85 Gm. of dextrose and 11.8 Gm. of ketone bodies. Her general clinical condition looked unsatisfactory, and we decided to resume the injections of insulin. For this reason, she was kept on both insulin and synthalin throughout February and March, when the study reported in table 2 was carried out.

Because of the greater severity of the condition, this patient ran a much more uneven course as far as glycosuria and ketonuria are concerned, and from the strictly experimental point of view, this case was not as suitable or

TABLE 3.—*Results of Study in Case 3*

		Urine			Diet				Synthalin, Mg.	
Period	Date	Volume, Cc.	Specific Gravity	Dextrose, Gm.	Carbohydrate	Protein	Fat	Sugar	A. M.	P. M.
I	2/11/27	1,335	1.021	20	99	75	150	...	..	..
	2/12/27	1,800	1.015	13	101	75	150	...	..	..
	2/13/27	1,800	1.015	13	100	75	150	...	..	..
	2/14/27	1,500	1.022	30	99	75	150	...	..	..
	2/15/27	1,900	1.018	19	100	75	149	...	..	..
	2/16/27	1,400	1.026	37	101	76	151	...	..	..
	2/17/27	1,500	1.021	22	99	75	151	...	..	..
	2/18/27	1,525	1.018	14	100	74	149	...	..	..
	Average per day.....			21						
II	2/19/27	1,400	1.019	7	100	75	150	...	25	25
	2/20/27	1,400	1.017	8	100	76	150	...	25	—
	2/21/27	2,300	1.015	11	100	75	149	...	—	25
	2/22/27	1,500	1.012	8	100	76	151	...	25	25
	2/23/27	1,250	1.018	6	100	75	150	...	—	25
	2/24/27	1,800	1.015	15	100	76	151	...	25	25
	2/25/27	1,425	1.012	ft. tr.	99	75	150	...	—	25
	2/26/27	1,150	1.015	6	101	75	150	...	25	25
	2/27/27	1,150	1.019	9	100	75	150	...	25	—
	Average per day.....			8						
III	2/28/27	1,600	1.020	29	99	75	150	...	..	..
	3/ 1/27	1,675	1.020	28	100	75	149	...	..	..
	3/ 2/27	1,400	1.021	22	101	64	148	184	..	..
	3/ 3/27	1,675	1.029	67	99	75	151	...	..	..
	3/ 4/27	1,700	1.021	27	100	74	149	...	..	..
	3/ 5/27	1,200	1.025	37	100	75	150	...	..	..
	3/ 6/27	1,500	1.027	48	100	75	150	...	..	..
	Average per day.....			37						

as convincing as the first, but sufficient corroborative evidence can be gathered from it. She was able to take larger doses of synthalin than the patient in case 1 without developing any marked gastric distress.

During the first period, which lasted from the 4th to the 16th of March, she received 20 units of insulin twice a day and 25 mg. of synthalin twice a day, as recorded in the chart. Throughout the whole period, glycosuria and ketonuria persisted. During the second period (from March 17 to 22), the synthalin was withdrawn. During the third period, the synthalin was added again. The results here can be judged only in a comparative way.

The total amount of sugar excreted during the first period of thirteen days of insulin plus synthalin therapy was 261 Gm., or 20 Gm. a day; whereas during the second period, the sugar excreted in six days on the same diet and insulin but without synthalin was 216 Gm. or 36 Gm. a day.

In the third period, the synthalin was added again, and we noticed a marked drop in the glycosuria and ketonuria; unfortunately, the study had to be prematurely interrupted because the patient left the hospital.

CASE 3.—D. K., a man, aged 39, had had diabetes for nineteen years, the last five of which had been spent in our service at the hospital. The course of his diabetic condition had always been comparatively mild. Glycosuria and hyperglycemia could be controlled by placing him on a diet of 75 Gm. of carbohydrate, 75 Gm. of protein and 150 Gm. of fat, without the aid of insulin.

On a diet of 100 Gm. of carbohydrate, 75 Gm. of protein and 150 Gm. of fat, he developed glycosuria, which could be controlled by 10 units of insulin administered twice a day.

The study in his case is divided into three periods and is recorded in table 3. During the first period (from February 11 to 19), he was kept on a diet consisting of 100 Gm. of carbohydrate, 75 Gm. of protein and 150 Gm. of fat, without insulin. On this diet, he excreted 168 Gm. of dextrose, or 21 Gm. a day, throughout the period of eight days.

During the second period (from February 19 to 28), he received synthalin in 25 mg. doses, as indicated in table 3. During this period of nine days, he excreted 70 Gm. of dextrose, or 8 Gm. a day.

During the third period (from March 1 to 7), the synthalin was withdrawn and glycosuria became much more marked. He excreted 258 Gm. in the seven days, or 37 Gm. a day.

CASE 4.—S. G., a woman, aged 53, had had diabetes for six years prior to admission to the hospital, during which period she lost 50 pounds (22.7 Kg.) in weight. On admission, the blood sugar concentration was 293 mg. per hundred cubic centimeters. Throughout the entire study, the patient was kept on a diet consisting of 75 Gm. of carbohydrate, 75 Gm. of protein and 150 Gm. of fat.

During the first period (from March 26 to 29), she was placed on a standard diet and was found to excrete an average of 26 Gm. of dextrose a day.

During the second period (from March 30 to April 13), the patient was given synthalin as described in table 4. During the first four days, there was practically no effect on the excretion of dextrose, but, beginning with the fifth day, the output dropped considerably and stayed low throughout the entire period. The average output of dextrose, not including the first four days, was 9 Gm. a day (including the four days the average output was 13 Gm. a day).

During the third period (from April 14 to 20), the synthalin was withdrawn. On the third day, there was a considerable rise in the excretion of dextrose which on the last day reached the highest figure, 35 Gm. The average daily output was 24 Gm., which corresponds closely with that of the foreperiod.

During the fourth period (from April 20 to May 1), synthalin was administered again. The excretion of dextrose decreased immediately and remained lower throughout the entire period. The average excretion of dextrose was 11 Gm. a day.

From May 2 to 9 (the fifth period), the synthalin was again withdrawn, and the excretion of dextrose rose to an average output of 28 Gm.

CONCLUSIONS DRAWN FROM THE FOUR CASES STUDIED

The four cases studied fairly represent all stages of severity in uncomplicated diabetes. Cases 3 and 4 were comparatively mild; case 1, moderately severe and case 2 very severe. The results obtained in these cases may be discussed from the physiologic and clinical aspects.

TABLE 4.—*Results of Study in Case 4*

Period	Date	Urine					Diet			Blood Sugar	Body Weight, Pounds	Synthalin, Mg.		Remarks
		Volume, Cc.	Specific Gravity	Dextrose, Gm.	Acetone	Nitrogen, Gm.	Carbohydrate	Protein	Fat			A. M.	P. M.	
I	3/26/27	2,375	1.012	28	0	....	76	76	150	293	117			
	3/27/27	1,600	1.020	27	0	....	75	75	151					
	3/28/27	1,900	1.016	19	0	....	75	76	150					
	3/29/27	2,575	1.019	30	0	....	75	75	150	...	118			
	Average per day			26										
II	3/30/27	1,700	1.019	29	0	....	75	75	149	305	...	12.5	12.5	
	3/31/27	1,825	1.016	23	0	....	75	76	151	...	119	12.5	12.5	
	4/ 1/27	1,960	1.016	23	0	....	71	75	151	...	...	12.5	—	
	4/ 2/27	2,420	1.014	23	0	....	75	76	150	...	...	25	25	
	4/ 3/27	1,120	1.013	8	0	....	74	33	101	...	...	25	—	Nausea after breakfast
	4/ 4/27	1,360	1.010	5	0	....	75	56	120	...	....	25	—	Anorexia before dinner
	4/ 5/27	1,300	1.012	7	0	....	74	59	139	...	117	12.5	12.5	Anorexia
	4/ 6/27	1,950	1.010	10	0	....	74	63	133	...	...	12.5	12.5	Anorexia
	4/ 7/27	1,850	1.011	14	0	....	75	76	149	...	...	12.5	—	
	4/ 8/27	1,650	1.012	7	0	....	76	76	151	...	118	25	—	
	4/ 9/27	1,760	1.010	8	0	....	75	75	151	...	...	12.5	12.5	
	4/10/27	2,440	1.010	12	0	....	75	75	151	...	...	—	10	
	4/11/27	2,060	1.009	12	0	....	75	76	150	...	...	10	25	
	4/12/27	1,710	1.011	8	0	....	75	75	150	...	119	25	—	
	4/13/27	1,840	1.011	10	0	....	71	74	149	...	...	25	20	
	Average per day			13										

III	4/14/27	1,700	1.012	11	0	7.1	70	56	124				
	4/15/27	2,350	1.019	16	0	7.9	75	76	151	...	119		
	4/16/27	1,760	1.014	29	0	8.5	75	76	149				
	4/17/27	2,290	1.013	25	0	9.8	75	75	150				
	4/18/27	1,980	1.012	26	0	8.9	75	75	150				
	4/19/27	2,370	1.015	35	0	11.3	75	75	150	...	119		
	Average per day.....			24									
IV	4/20/27	1,300	1.012	12	0	7.1	74	54	125	300	...	12.5	12.5	
	4/21/27	2,070	1.011	17	0	9.2	75	75	150	...	...	12.5	12.5	
	4/22/27	1,840	1.009	12	0	5.7	75	75	150	...	120	—	12.5	
	4/23/27	2,120	1.009	11	0	8.2	74	75	149	...	...	25	12.5	
	4/24/27	2,350	1.010	13	0	10.8	75	75	150	...	...	—	12.5	
	4/25/27	1,930	1.011	9	0	10.2	75	75	151	322	...	25	12.5	
	4/26/27	1,630	1.013	14	0	7.9	75	56	124	...	...	25	—	
	4/27/27	2,190	1.010	8	0	8.9	75	70	148	...	...	25	12.5	
	4/28/27	1,690	1.010	8	0	6 9	75	51	121	...	119	25	25	Anorexia before dinner
	4/29/27	1,910	1.008	7	0	7.1	75	76	149	...	...	—	25	
	4/30/27	1,550	1.012	8	0	7.3	76	74	149	...	...	25	25	
	5/ 1/27	1,380	1.010	8	0	7.3	75	74	150	...	...	—	25	
	Average per day.....			11										
V	5/ 2/27	1,580	1.010	12	...	8.4	75	55	124	...	...	....	....	Anorexia
	5/ 3/27	1,740	1.014	22	...	8.7	75	74	150	273	118			
	5/ 4/27	1,960	1.012	22	ft.tr.	8.4	76	76	149					
	5/ 5/27	2,140	1.020	47	tr.	11.0	75	76	151					
	5/ 6/27	2,180	1.015	36	ft.tr.	10.7	75	76	150	...	119			
	5/ 7/27	2,400	1.015	34	0	11.8	75	75	151					
	5/ 8/27	1,830	1.016	29	0	10.9	75	74	150					
	5/ 9/27	1,740	1.013	18	0	....	75	75	151					
	Average per day.....			28										

Physiologic Results.—Effect of Synthalin on Glycosuria: The study of the influence of any drug on the sugar output in the urine must be made with the full realization that the results are of value only if we know what the food intake is, and that the patient has continued on the same diet before and after the drug has been administered, so that we have a fore and after period. The sugar output in the urine in all diabetic patients represents the difference between the tolerance and the dextrose-forming material ingested. In all of our cases, careful attention was paid to the maintenance of a standard diet throughout the tests, to the patient's consumption of all of the food given and to proper control periods before and after the administration of the synthalin.

An analysis of the tables shows that synthalin is capable of reducing the sugar output in the urine in all the cases that we studied. The patient in case 1 received synthalin during the second, fifth, seventh, ninth and eleventh periods, the last period extending to the date this article was written. During the early periods, this patient suffered considerable gastro-intestinal distress, which manifested itself by pressure in the epigastrium after meals, anorexia, nausea, vomiting and diarrhea. Because of these symptoms, the patient could not consume all of her food, and that in itself might have been sufficient to cause a drop in her urinary sugar. But in the later periods, when gastric disturbances did not occur, the results are cleancut and convincing. The results during the fifth, seventh, ninth and eleventh periods can be ascribed only to synthalin therapy. Since May 28, the patient has excreted traces of sugar only occasionally, being free from sugar most of the time.

Cases 2, 3 and 4 corroborate the observations in case 1 in that during the periods when synthalin was administered there was diminution in the excretion of sugar.

Influence of Synthalin on Blood Sugar Concentration: In their first communication, Frank, Nothmann and Wagner [1] report their experiment on a normal rabbit in which the subcutaneous administration of 3 mg. of synthalin per kilogram of body weight produced a drop in the blood sugar from 131 to 57 mg. Oral administration of 50 mg. to a fasting rabbit, weighing 1 Kg., caused a drop in the blood sugar from 159 to 70 mg. and hypoglycemic symptoms, which were counteracted by the injection of dextrose.

We repeated those experiments on normal rabbits, and the following results were obtained.

PROTOCOLS

Rabbit 1.—This animal weighed 2.5 Kg. The blood sugar was 120 mg. per hundred cubic centimeters after fasting for eighteen hours.

11:30 a. m. One hundred milligrams of synthalin was given by mouth.

4:30 p.m.: The blood sugar was 77 mg.

6:10 p. m.: The animal looked sick. Ten cubic centimeters of 16 per cent dextrose solution was given intravenously. In a few minutes, the animal appeared better.

Midnight: The animal was found dead in its cage.

RABBIT 2.—This animal weighed 2.85 Kg.

11:10 a. m.: The fasting blood sugar was 157 mg. per hundred cubic centimeters. One hundred milligrams of synthalin was given by mouth.

3:15 p. m.: The blood sugar was too low to make a determination. The animal appeared limp; 10 cc. of dextrose was given intravenously; recovery resulted.

6:10 p. m.: The animal again appeared limp.

6:30 p. m.: Ten milligrams of dextrose was given. The animal improved remarkably.

Midnight: The animal was found dead in its cage.

RABBITS 3 and 4.—These animals were treated in the same way as were rabbits 1 and 2, except that they received 25 mg. of synthalin subcutaneously. Within from four to five hours, both developed hypoglycemic symptoms, the blood sugar in the latter dropping to 51 mg. Both animals had convulsions, from which they recovered after the intravenous administration of dextrose. Both animals, however, ultimately died from their hypoglycemic condition.

We administered synthalin to another series of rabbits, not in lethal doses, but in amounts that would correspond to therapeutic doses.

RABBIT 5.—This rabbit weighed 2.7 Kg. Eighteen hours after his last meal, he had a blood sugar concentration of 125 mg. per hundred cubic centimeters.

Jan. 26, 1927, 10:45 a. m.: Five milligrams of synthalin was given by mouth.

4:15 p. m.: The blood sugar was 118 mg.

January 27, 11:00 a. m.: The blood sugar was 123 mg.

Midnight: Ten milligrams of synthalin was given by mouth.

11:00 p. m.: The blood sugar was 111 mg.

January 28, 10:30 a. m.: Thirty milligrams of synthalin was given by mouth.

6:00 p. m.: The blood sugar was 104 mg.

January 29, 10:00 a. m.: The blood sugar was 110 mg.

This animal fasted throughout the entire period; in spite of this, he did not show a material drop in the blood sugar concentration.

RABBIT 6.—This animal weighed 2.7 Kg. and was treated in a manner similar to that in which rabbit 5 was treated, having been given 5, 10 and 35 mg. of synthalin on three successive days. Its blood sugar throughout those four days was 114 Gm., 111 Gm., 111 Gm., 92 Gm., 117 Gm. and 101 Gm., at the last determination.

RABBIT 7.—This rabbit weighed 2.33 Kg.

Feb. 17, 1927, 10:45 a. m.: The blood sugar was 121 mg.

11:30 a. m.: Thirty-five milligrams of synthalin was given by mouth.

5:00 p. m.: The blood sugar was 125 mg.

February 18, 11:00 a. m.: The blood sugar was 63 mg. The animal looked ill, and a grunting respiration was heard. Ten cubic centimeters of 10 per cent dextrose solution was given intravenously. The animal improved.

RABBIT 8.—This rabbit weighed 2.2 Kg.; while fasting, his blood sugar was 118 mg. He was then given 35 mg. of synthalin. Six hours later, his blood sugar was 124 mg., and the following morning it was 76.

These experiments prove that with large doses of synthalin one can bring about a definite hypoglycemic reaction, from which the animal can be made to recover temporarily by the administration of dextrose. The giving of more moderate doses (35 mg.) brought about a hypoglycemic effect in two animals and failed to give any results in two others.

The influence of synthalin on the blood sugar curve was studied in a patient with mild diabetes (Mrs. D.) on our service. Table 5 shows the results.

An examination of the blood sugar curve of this patient after the administration of 25 and 50 mg. of synthalin shows a drop in the blood sugar concentration to the range of normal within eight hours. In interpreting these results, however, the element of fasting must be considered.

TABLE 5.—*Results of Study on a Mild Diabetic Patient*

Date	Time	Blood Sugar	Synthalin	Comment
1/14/27	7:30 a. m.	173	.....	Fasting
	7:35 a. m.	...	25 mg.	
	10:15 a. m.	170	.....	Fasting
	2:10 p. m.	146	.....	Fasting
	5:30 p. m.	137		
3/10/27	9:00 a. m.	170	.....	Fasting
	9:05 a. m.	...	50 mg.	Fasting
	1:00 p. m.	151	.....	Fasting
	5:00 p. m.	117	.....	Regular supper
3/11/27	9:30 a. m.	126		

In the four cases that we studied at length, case 1 showed a definite reduction in the blood sugar (eighth period), though not at the same level at which it was kept when the patient received insulin.

In case 4, on the other hand, the patient did not show an appreciable change in the figures for blood sugar, although there was a difference in the dextrose output in the urine.

In summarizing, we may therefore state that the effect of synthalin on blood sugar concentration is variable, probably depending on some extraneous factor.

Influence of Synthalin on Protein Metabolism: The protein metabolism was studied in cases 1 and 4. During the ninth period in case 1, the total nitrogen excreted during six days was 70.8 Gm., or an average of 11.8 Gm. a day. Synthalin was not given during this period. When synthalin was administered during the tenth period, the total nitrogen excreted in eleven days was 100.6 Gm., or an average of 9.1 Gm. a day.

During the third period in case 4, without the administration of synthalin, 53.5 Gm. of nitrogen was excreted in six days, or 8.9 Gm. a day. During the twelve days of the fourth period, when synthalin was administered, the patient excreted 96.6 Gm., or 8.05 Gm. on an average;

whereas during the after-period of seven days when synthalin was not given, she excreted 69.9 Gm., or 9.9 Gm. a day.

These two cases seem to show a diminution in the nitrogen output during the period in which synthalin was administered. An explanation can probably be found in the sparing effect on the protein metabolism of the extra carbohydrate that is utilized.

Influence of Synthalin on Ketonuria: That the feeding of synthalin favorably affects the course of ketonuria is demonstrated conclusively in case 1 (sixth, seventh, eighth and ninth periods). During the sixth period, when synthalin was not given, the patient developed marked glycosuria up to 25 Gm. a day and ketonuria up to 2 Gm. of acetone bodies. Immediately after the administration of synthalin (the seventh period) the glycosuria and ketonuria began to subside, and on the ninth day of its administration the urine became ketone-free. In the eighth period, the synthalin was withdrawn, and the ketonuria immediately returned, reaching 1.5 Gm. of acetone bodies on the ninth day. The return to synthalin during the ninth period again caused its disappearance.

The effect of synthalin in case 2, though apparent, is not so dramatic as in case 1. In case 2, the condition was much more severe, and in order to free the patient entirely from ketonuria, we would probably have had to administer much larger doses than we cared to give for fear of gastric disturbance. The results in the third period are striking, and it is much to our regret that the study could not be concluded because the patient insisted on leaving for home.

Influence of Synthalin on Combustion of Dextrose in the Diabetic Patient: Direct proof that synthalin causes the combustion of dextrose in diabetes can be established only by determining the respiratory quotient. It has not been done in this work. We have, however, succeeded in demonstrating the complete disappearance of glycosuria in case 1 and the diminution of the sugar output in all of the other cases. These cannot be explained on any other basis. Retention of sugar would be followed by marked hyperglycemia, which is not noticeable; on the contrary, diminution in the blood sugar is more common.

Corroborative physiologic evidence of the theory that the dextrose is burnt during the administration of synthalin can be seen from the observation that ketonuria disappeared completely (case 1) or became considerably diminished (case 2, third period). This phenomenon can be explained only on the assumption that the dextrose acted antiketogenetically during combustion. Reduction in the nitrogen output running parallel with a diminished or disappearing glycosuria during the synthalin periods lends additional support to the theory that the synthalin causes combustion of the dextrose in a diabetic patient.

CLINICAL COMMENT

In treating patients with diabetes, one must fulfill certain requirements. The patient must be given a sufficient amount of protein to enable him to maintain nitrogenous equilibrium, a sufficient amount of fat to cover the caloric requirements and enough carbohydrate to prevent the development of ketonuria.

The condition in the great majority of diabetic patients can be controlled by merely prescribing the necessary amount of food required. In the more severe cases, this can be accomplished only with the aid of insulin. There are a large number of patients in this category who would rather have moderate hyperglycemia and glycosuria than submit to daily hypodermic injections of insulin. However, patients who develop ketonuria do not have any choice; they must take insulin or run the risk of acidosis and coma.

Insulin is the ideal drug for these patients because it clears up hyperglycemia, glycosuria and ketonuria, it alleviates all the symptoms of diabetes and improves the patient's nutrition and general well-being.

From the physician's point of view, insulin answers all requirements and has only one disadvantage, that of possible hypoglycemic reactions. From the patient's point of view, the necessity for frequent hypodermic injections constitutes a serious disadvantage. For this reason, the diabetic public looks with eagerness to biologic chemists for the discovery of a remedy which possesses the therapeutic effect of insulin but which can be administered more easily.

A survey of the action of synthalin in our cases seems to show that its discoverers have made a tremendous step in the right direction. This substance is capable of clearing up or diminishing glycosuria and ketonuria when administered in tablet form by mouth. This is a decided advantage from the patient's point of view. The possibility of gastric distress setting in is an annoying feature, but a survey of case 1, in which the patient was the greatest sufferer in the early stages, seems to show that there is a possibility of establishing a tolerance or immunity toward it. During the later periods, she did not complain. In cases 2, 3 and 4, serious gastric discomfort did not occur even in the beginning of the tests. In a number of other cases the use of synthalin, starting with doses of 25 mg., produced gastric difficulties which immediately discouraged the patients. Whether such sensitive people would gradually develop gastric tolerance for the drug can be determined only by further study. Patients who have objections to synthalin may therefore be advised to exercise a little perseverance before discontinuing its use.

In a recent publication, Adler [3] advises the administration of 0.5 Gm. of a sodium salt of dehydrocholic acid, which is an oxidation compound

3. Adler: Nebenwirkungen des Synthalins, Klin. Wchnschr. **6**:493, 1927.

of cholic acid. This acts as a bile stimulant, and Adler claims that therefore it eliminates the unpleasant gastric disturbance after the administration of synthalin. We have not yet had an opportunity to test the efficacy of such medication, but we expect to do so shortly.

From the physician's point of view, synthalin has another disadvantage as compared with insulin; its action is not prompt. In one case, it took four days before any effect was noticeable; this characteristic precludes its being used in cases of emergency. In simple cases of diabetes in which the use of insulin is not desired, however, synthalin may be tried.

OCCURRENCE OF HYPERSENSITIVENESS OR ALLERGY IN FIVE GENERATIONS OF ONE FAMILY*

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ST. LOUIS

The basis of this paper is a study of the occurrence of allergic manifestations in the E. Family, including the direct descendants of W. G. E. (1) and A. A. E. (2). The study includes observations on eighty-seven persons and five generations. Certain introductory statements should be made. The genealogical chart shows that W. G. E. (1) was the son of first cousins and that he married the first cousin of both his parents; hence, a considerable reinforcement of inherited characters must have occurred in the f-1 generation. W. G. E. (1), his wife, A. A. E. (2), and his sister, C. E. L. (0), were all hypersensitive. Information cannot be obtained concerning allergic manifestations in their parents. A. A. E. (2) and W. G. E. (1) had fourteen children, of whom nine died in early life. It has not been possible to obtain histories of these nine children other than the causes of death. They are therefore omitted from the numerical counts. They did not have any descendants.

The husbands and wives of the direct descendants have been used as controls, that is, a group of unselected persons, presumably of non-allergic stock.

The investigation was carried on entirely by correspondence; a questionnaire was sent for each member of a family group to the head member of that group. There were twenty-two such groups. The questionnaires were carefully and intelligently filled out in every case; about four weeks elapsed between the sending of the questionnaires and the return of the last set of answers. I have interpreted as correctly as possible the answers obtained, which formed the material for this work. This was not always easy, and errors have probably occurred in respect to both positive and negative observations.

Six well recognized forms of allergic reaction have been selected: asthma, hay-fever, vasomotor rhinitis, urticaria, angioneurotic edema and eczema.

The criteria by which the reported data have been evaluated are given in the following section.

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* From the Department of Internal Medicine, Washington University School of Medicine.

CRITERIA OF EVALUATION FOR REPORTED DATA

Asthma.—Asthma was not common in the E. family. There were only four cases. The cases of E. C. E. (74) and J. G. E. (91) were mild and occurred only in connection with severe attacks of hay-fever. One severe case occurred in a child, aged 5 years, J. W. E. (42). His mother, one of the control group was hypersensitive and was also subject to asthma. One of her other children had attacks of asthma associated with food allergy.

Hay-Fever.—There were several severe cases and more mild cases of hay-fever.

Vasomotor Rhinitis.—The term vasomotor rhinitis is used in referring to occasional attacks of coryza and sneezing apparently in the absence of infection. Under this classification is included a peculiar

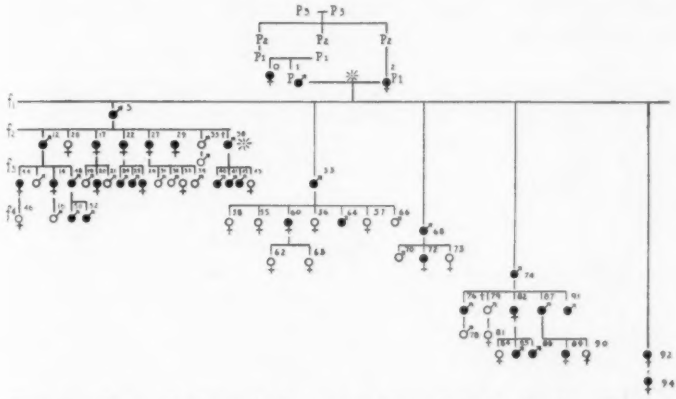

Chart 1.—Cases of allergy in five generations of the E. family. The hypersensitive persons are shown in black. The asterisk indicates double inheritance, the dagger, negative inheritance; in all other families one parent was hypersensitive.

manifestation which occurred in nine members of the family. This consisted of spells of sneezing, which came on without warning, any time during waking hours. R. E. S. (92) sneezed violently from nineteen to twenty-seven times, at intervals of from thirty to forty-five seconds, with profuse nasal discharge and tearing. C. R. E. (68) sneezed from fifteen to twenty times, and his daughter, M. M. E. (72), sneezed from ten to twelve times. Both W. G. E. (1) and A. A. E. (2) had these attacks, and three of their children have had them.

Urticaria.—Some difficulty was encountered in making statistics of subjects with this eruption as nearly all reported that they had had "hives" or something supposed to be "hives" during their youth. I have

eliminated the doubtful cases and usually include only those attributable to some known cause. Urticaria as a sole positive symptom is used only in the case of young children with a definite history.

Angioneurotic Edema.—Several interesting cases of angioneurotic edema are reported, with definite known causes.

Eczema.—The infantile form of eczema had been prevalent in one branch of the family. One or two cases existed in adults.

ANALYSIS OF DATA

The collected data have been arranged in charts and tables. Chart 1 shows the five generations of the E. family with the allergic members indicated. Chart 2 furnishes an analysis of the occurence of each separate manifestation of allergy. It specially emphasizes the fact that the cases of a given form of allergy tend to occur in persons closely related, rather than at random throughout the family. Only two or three cases occurred outside the small family groups.

TABLE 1.—*Numerical Summary of Cases and Analysis by Generations*

Generation	Number of Persons	Positive Cases	Controls	Positive Controls
P	3	3	..	..
f-1	5	5	5	0
f-2	24	14	15	1
f-3	28	12	3	0
f-4	4	2	..	..
Total	64	36	23	1

Table 1 is a numerical summary of the number of persons in each generation and the number of positive cases. The distribution of the controls is shown by generations, the one positive case occurring in a person of the f-2 generation.

Table 2 is an analysis of the cases according to the presence or absence of allergy in the parents. There were two families with both parents allergic, sixteen families with one parent allergic and two with neither parent allergic.

Table 3 is a classification according to the form of clinical manifestation, showing the number of cases of each form in each generation, and the total number of each form occurring in the family.

COMMENT

Many writers express the belief that asthma is hereditary. Among the earlier authorities on this question are Cullen [1] and Andral,[2]

1. Cullen: Practice of Physick, ed. 4, Edinburgh, 1784, p. 387.
2. Andral, G.: Cours de pathologie, ed. 3, Brussels, 1865.

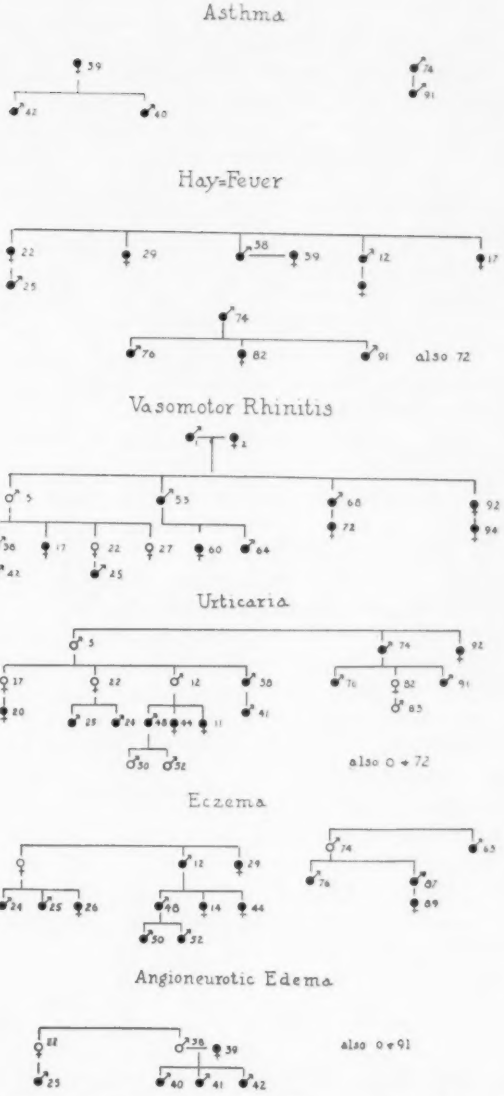

Chart 2.—Showing tendency for given forms of allergic manifestation to occur in groups of persons closely related.

Geddings [3] in Pepper's "System," 1883, quoted Salter, Ramadge and Steavenson on the hereditary tendency in asthma. In his original description of the "exudative diathesis" with which hypersensitiveness is associated, Czerny [4] noted the tendency of asthma to occur in families. "Protein sensitivity" was said to be hereditary by Osler, Longcope,[5] Cooke [6] and others.

TABLE 2.—*Analysis of Cases According to Presence or Absence of Allergy in the Parents*

Serial Number Parents	Children	Positive	Per Cent Positive
Double Inheritance—Both Parents Positive			
1 and 2	5	5	100
38 and 39	4	3	75
Single Inheritance—One Parent Positive			
5	8	6	75
53	7	2	28
68	3	1	33
74	5	4	80
92	1	1	100
12	4	3	78
17	3	1	33
22	3	3	100
27	4	0	0
60	2	0	0
76	1	0	0
82	3	1	33
87	2	1	50
44	1	0	0
14	1	0	0
48	2	2	100
Total	50	25	50
Negative Inheritance—Neither Parent Positive			
79	1	0	0
35	1	0	0

TABLE 3.—*Analysis of the Occurrence of Allergic Phenomena by Generations*

Generation	Form of Manifestation of Allergy					
	Asthma	Hay-fever	Vasomotor Rhinitis	Urticaria	Angioneurotic Edema	Eczema
P	..	..	2	1	1	..
f-1	1	1	3	2	..	1
f-2	1	8	8	4	1	4
f-3	2	2	2	8	4	7
f-4	..	..	..	2	..	2
Total	4	11	15	17	6	14

3. Geddings: Bronchial Asthma in Pepper: System of Medicine, 1883, vol. 3, p. 190.

4. Czerny, A.: Die exudative Diathese, Jahrb. f. Kinderh. **61**:199, 1905.

5. Longcope, W. T.: The Sensitivity of Man to Foreign Proteins, Harvey Lecture, 1916.

6. Cooke, R. A., and Vander Veer, A.: Human Sensitization, J. Immunol. **1**:201, 1916.

The term "hereditary" is often used by clinicians as applied to a disease which tends to appear in several members of the same family. Heredity in the biologic sense may not be involved. The study of heredity in man is a matter of considerable difficulty, and it is not certain that heredity in a human being follows the same comparatively simple laws and mechanisms that have been worked out for heredity in certain plants and lower animals. Some investigators, assuming that the mendelian laws can be applied to heredity in man, have studied the problem of hypersensitiveness from this standpoint. Drinkwater,[7] Cooke and Vander Veer [6] and Cooke and Spain [8] attempted to show that sensitization to protein is a true hereditary character following mendelian principles. In an extensive study of heredity in human conditions, Buchanan [9] failed to find evidence that asthma and "protein sensitivity" were dependent on a true hereditary factor.

According to Buchanan,[9] in seventeen families in which one parent had asthma, 102 children did not have asthma and eight had asthma; and in thirty-six families in which neither parent had asthma, 226 children did not have asthma and forty-six had asthma. Working on the problem of hypersensitiveness to proteins, in seven families with one parent sensitive, he found thirty-six children not sensitive and two sensitive. In twenty-four families without protein sensitization in either parent, 126 children were not sensitive and twenty-eight children were sensitive. He states that if a character is hereditary, the laws of heredity must hold in 100 per cent of the cases, and that the factor either is or is not present. This is undoubtedly true as the behavior of hereditary characters is understood. But in such a condition as hypersensitiveness (which includes asthma as one of its manifestations), the difficulties in obtaining a perfect agreement with the mendelian ratios are great. The greatest care in taking histories may not result in accurate information, especially in the relatives of patients. Human families are not large enough to give a complete picture of the possible combinations of factors. Only in a large number of offspring can a close approximation to the 3:1 ratio be expected. In such a condition as hypersensitiveness to proteins there is always the possibility that a person having the factor of hypersensitiveness may not have manifested the tendency at all, or that he may have manifested it in a form which he could not recognize or remember. In young children, the factor may exist, but not show as a clinical state later in life. Cooke and Vander Veer, and Cooke and Spain

7. Drinkwater, H.: Mendelian Heredity in Asthma, Brit. M. J. **1**:88, 1909.

8. Cooke, R. A., and Spain, W.: Studies in Specific Hypersensitiveness: IX. The Familial Occurrence of Hay-Fever and Bronchial Asthma, J. Immunol. **9**:521, 1924.

9. Buchanan, J. A.: Heredity and Human Conditions, Am. J. M. Sc. **165**:675, 1923.

endeavored to obviate this last difficulty by estimating the number of children who would manifest hypersensitiveness at some time later in life, from certain curves based on the average age for the appearance of manifestations in different kinds of inheritance. This estimate has not been attempted in the group under consideration in this paper.

In a study of heredity in man, certain principles must be laid down as a working basis. A character which is truly hereditary is dependent on the chromosomal make-up of the germ plasm. Such a character is always associated with a contrasted character, and one is dominant over the other: that is, when genes for both characters are present in the same person, the dominant one is evident, while the other is concealed. The mendelian laws deal with the behavior of these genes. In this discussion the existence of the two characters "hypersensitive" and "not hypersensitive" has been assumed. As will be seen, it is not easy to decide which should be considered "dominant" and which "recessive."

If "hypersensitive" is the dominant factor the following results from the six possible varieties of mating may be expected:

DD × DD—offspring all hypersensitive.
DD × DR—offspring all hypersensitive.
DD × RR—offspring all hypersensitive.
DR × DR—75 per cent of offspring hypersensitive.
DR × RR—50 per cent of offspring hypersensitive.
RR × RR—no hypersensitive offspring.

If "hypersensitive" is the recessive factor:

DD × DD—no offspring hypersensitive.
DD × DR—no offspring hypersensitive.
DD × RR—no offspring hypersensitive.
DR × DR—25 per cent of offspring hypersensitive.
DR × RR—50 per cent offspring hypersensitive.
RR × RR—all offspring hypersensitive.

Assuming that "hypersensitive" is the dominant factor, three kinds of matings can be determined in the E. family.

1. When both parents are hypersensitive, DD × DD, DD × DR or DR × DR are the resultant combinations. In the first two matings, one would expect 100 per cent of the children to be hypersensitive; in the third 75 per cent. Actually, one finds two families with both parents hypersensitive. The five childen of W. G. E. (1) and A. A. E. (2) were all hypersensitive. It is improbable, however, that either W. G. E. (1) or A. A. E. (2) were DD because there is not any evidence of a DD parent among the members of the f-1 generation, as shown by 100 per cent hypersensitive offspring in one family of children. A. A. E. (2) and W. G. E. (1), as well as T. L. E. (38) and S. W. E. (39), must represent the DR × DR type of mating. There

were nine children in these two families, eight of whom were hypersensitive. The only nonhypersensitive case occurred in a baby less than 1 year of age.

2. When one parent is hypersensitive, DD × RR or DR × RR are the resultant combinations. DD × RR probably does not occur, for reasons explained in the preceding paragraph. DR × RR gives an expectation of 50 per cent hypersensitive offspring, which is the figure obtained in the E. family.

3. When neither parent is hypersensitive, RR × RR is the resultant combination. Only two such families had children. In each family there was one child and neither of the children was hypersensitive.

The observations in the E. family agree well with the expected figures for a dominant factor, but the number of cases is too small for one to draw conclusions.

TABLE 4.—*Results in E. Family with "Hypersensitive" as Dominant Factor*

Summary of Matings	Theoretically Hypersensitive	Actually Hypersensitive
DR × DR	75%	88.8%
DR × RR	50%	50%
RR × RR	0	0

TABLE 5.—*Results in E. Family with "Hypersensitive" as Recessive Factor*

Summary of Matings	Theoretically Hypersensitive	Actually Hypersensitive
RR × RR	100%	88.8%
RR × DR	50%	50%
DR × DR	25%	0

Assuming that "hypersensitive" is a recessive factor, the possibilities and actual observations are summarized in table 5.

Although the actual figures are not greatly at variance with the theoretical figures, it is difficult to interpret the hypersensitive factor as a recessive characteristic, because it would then be necessary to postulate a factor for "hypersensitive" in both parents whenever there is a hypersensitive child.

Table 6 gives the percentages of hypersensitive offspring obtained by Drinkwater [7] in a family of asthmatic persons, reported in 1909. It shows also the results of Cooke and Spain in 1,889 cases reported in 1924.

The evidence from the three sets of figures seems to point to an inherited character as the basis for naturally occurring allergy, probably a dominant factor. Two points in favor of this interpretation are:

1. Not all the children with two hypersensitive parents can be shown to be hypersensitive, as is necessary in case the character is recessive.

2. In order to have any hypersensitive children in the case of single inheritance, if the character is recessive, it is necessary that the nonhypersensitive parent carry the recessive factor for "hypersensitive." Therefore, every one of the eleven persons who married hypersensitive members of the E. family and had hypersensitive offspring must have been of hypersensitive families. Only two of them had family histories of hypersensitiveness, and only one of the two was hypersensitive.

The 41.1 per cent found by Cooke and Spain [8] to be hypersensitive persons with neither parent hypersensitive cannot be reconciled with the interpretation as a dominant factor. In working from a single patient to the histories of his relatives, however, it is not always possible to get accurate information, and some cases of hypersensitiveness in parents might be missed.

TABLE 6.—*Percentages of Positive Cases in Families Studied by Drinkwater, Cooke and Spain and of Those in the E. Family*

	Double Inheritance	Single Inheritance	Negative
Drinkwater, 20 cases	.....	50%	0
Cooke and Spain, 1,889 cases	69.4%	58%	41.1%
E. family	88.8%	50%	0
Expected ratio, dominant character	100% or 75%	50%	0
Expected ratio, recessive character	100%	50%	25%

In interpreting the hypersensitive tendency as a dominant hereditary character, I agree with Cooke and Spain,[8] but differ with Adkinson,[10] who has interpreted it as a recessive factor. The 41.1 per cent of hypersensitive persons with neither parent hypersensitive favors this interpretation, as under these circumstances 25 per cent of the offspring may be expected to show the character.

If the character is hereditary, as is understood in the biologic sense, either the absence of 100 per cent incidence in double inheritance or the presence of 41.1 per cent incidence in negative inheritance must be wrong, according to the conditions laid down for a true inherited character.

The reasons for the discrepancies here encountered have already been discussed. The conclusion, therefore, that such a character as "hypersensitive" exists but that it is dominant cannot be made. However, the transmissibility of the allergic tendency from parent to child appears to be demonstrated conclusively.

10. Adkinson, J.: Bronchial Asthma as an Inherited Character, Genetics, **5**:365, 1920.

SUMMARY

1. A family of ninety-four persons and five generations was studied by means of histories obtained through questionnaires, in regard to the hereditary occurrence of allergic manifestations. The manifestations of allergy considered were: asthma, hay-fever, vasomotor rhinitis, urticaria, angioneurotic edema and eczema.

2. Twenty-three persons who were married to members of the E. family have been used as controls. As a group of unselected normal patients, their histories were taken in the same manner as the histories of the E. family.

3. In the E. family, 56.2 per cent of the members were allergic. Among the twenty-three controls, not related to the family except by marriage, only one was allergic.

4. The results of this survey support the contention that allergy is familial in distribution.

5. Given forms of allergic manifestation apparently tend to be prevalent among closely related persons.

HEMOCIDAL PROPERTIES OF THE BLOOD SERUM

WITH SPECIAL REFERENCE TO PERNICIOUS ANEMIA

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Notwithstanding the fact that increased destruction of blood in pernicious anemia was demonstrated over thirty years ago by Hunter,[1] it would appear from a careful search of the literature that a direct destructive action of the blood serum on the red corpuscles in this disease has not been demonstrated. The bulk of the research on the mechanism of erythrocyte destruction in pernicious anemia appears to have been directed toward the demonstration of a localization of the process in certain organs, especially in the bone marrow, spleen, hemolymph nodes and liver. The investigations have been carried out principally along three different lines of pursuit: (1) histologic studies of the phagocytic activity of the cells of the different organs, (2) the quantitative determination of the iron content of these organs, and (3) the isolation of hemolytic substances from these organs.

Hunter found excessive deposits of pigment in the cells of the livers of persons dying of pernicious anemia, and so convinced was he that the liver is the principal site of cell destruction, that he concluded that the causative agent of the disease must be of intestinal origin. Dickson [2] showed that the bone marrow is the site of extensive phagocytosis of red corpuscles, not only in pernicious anemia, but also in other severe chronic anemias and in certain acute infections associated with a leukopenia. He was of the opinion that the bone marrow is the principal site of erythrocytoclasis in pernicious anemia.

In a more recent article, Schneider,[3] while, of course, not denying the existence of phagocytosis in the spleen, is of the opinion from histologic studies of spleens made by him in association with Eppinger in the Von Noorden Clinic, that the actual hemolysis (escape of hemoglobin) takes place in the Kupffer cells of the parenchyma of the liver.

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1. Hunter, William: Pernicious Anemia, Charles Griffin & Company, 1901, p. 77; Severest Anemias, London, 1909, p. 110; Brit. M. J. **2**:81, 1890; Lancet **1**: 287, 1890; **1**:283, 1903.

2. Dickson: The Bone Marrow, New York, Longmans, Green and Company, 1908, p. 73.

3. Schneider, J. P.: The Splenic Pathology of Pernicious Anemia and Allied Conditions, Arch. Int. Med. **17**:32 (Jan.) 1916; Journal-Lancet **37**:105, 1917.

None of the investigations has disclosed anything peculiar to the phagocytosis that occurs in pernicious anemia, and Warthin [4] concluded that cell destruction in pernicious anemia differs only quantitatively from that which occurs normally. Dickson states that the phagocytic cells of bone marrow arise from endothelial lining of blood capillaries and from adenoid reticulum of the marrow. "Pigment cells and cells containing erythroblasts and red corpuscles are seen in very great numbers in the bone marrow whenever there is any great amount of blood destruction going on in the organism. This is seen in pernicious anemia and other long-standing anemias; also seen in equal and even greater numbers in acute diseases, especially septicemias and pneumonias with leucopenia. I therefore regard the marrow as one of the principal sites of hemolytic action, scarcely, if at all of less importance, in the carrying on of this function than are the liver and spleen, a fact which is all the more striking when the great extent and the wide distribution of the red bone marrow throughout the body is borne in mind."

Warthin [4] reported eight cases of pernicious anemia, including postmortem examination, in which he found changes in both the lymph and hemolymph nodes which varied greatly in degree. In only one case did the peripheral glands (axillary, superficial cervical, inguinal and cubital) show any change that could be regarded as belonging essentially to pernicious anemia; also the changes in the mesenteric glands were not constant, occurring only in two cases. In all eight cases he found changes in the prevertebral, retroperitoneal and cervical lymph and hemolymph glands indicating excessive hemolysis. These changes were: an apparent increase in the number and hyperplasia of resting hemolymph glands; dilatation of the blood sinuses, with an increase in the number of phagocytes containing disintegrating red cells and pigment; and in the lymph gland, dilatation of the lymph sinuses, presence of increased number of red blood cells in the latter, an increased number of phagocytes and congestion. The difference in degree of changes suggests intermittent hemolysis. In some cases, very little hemosiderin or few phagocytes containing red blood cells are found in the spleen, while they are abundant in the hemolymph glands and vice versa.

The hemolytic poison does not confine itself to the portal areas as claimed by Hunter, but is present in the general circulation. Furthermore, as pointed out by Hunter, the hemolysis of pernicious anemia is a cellular process and is performed by the phagocytes of the spleen, lymph glands, hemolymph glands and bone marrow in response to the direct stimulus of the poison or of blood cells injured by the poison. He did not find any evidence of hemolysis in the liver in his eight cases. He thinks the hemolysis of pernicious anemia does not differ in kind from that which occurs in other diseases but that the difference is one of

4. Warthin, A. S.: Am. J. M. Sc. **124**:674, 1902; J. M. Research **7**:435, 1902.

degree only. Lymphoid and megaloblastic changes in the marrow do not form an essential part of the pathologic processes in pernicious anemia and are to be regarded as of a compensatory nature—an increased activity of red blood cell formation occurs to supply the deficiency caused by the excessive hemolysis.

Determinations of the iron content of the organs offer a less satisfactory source of evidence than does phagocytosis regarding the localization of the process of cell destruction, as the iron content of an organ presumably depends to some extent on the rate of utilization of iron for the purpose of manufacturing of red cells. Queincke [5] found the iron content of the liver below normal in cases of excessive loss of blood from the body, and Muir and Shaw Dunn [6] found that the excess of iron stored in the organs of rabbits following acute anemia caused by injection of hemolytic serum was almost entirely absorbed by the time complete regeneration of blood had taken place; the absorption from the cells of the liver was almost complete, but a certain excess remained in the splenic pulp and in the renal cortex.

Hunter, however, was convinced that the characteristically high values found by himself and others for iron content in the liver in pernicious anemia was evidence of a localization of the process of cell destruction in that organ. Schneider interpreted the marked urobilinocholia which he observed in pernicious anemia as evidence of excessive destruction of red cells in the liver. Ryffel [7] has determined the iron content in six cases of pernicious anemia. In five of these cases, the liver and spleen showed a higher iron content than that found in normal cases; usually the iron content of the liver (in weight per cent) was higher than that of the spleen, kidney or heart (from 0.24 per cent to 1.01 per cent in the liver; the normal weight for the liver is about 0.10 per cent). Unfortunately, the normal weight (as they considered it) is not stated in any of their investigations.

The reported results of attempts to isolate hemolytic substances from the organs in pernicious anemia have been inconsistent and difficult of interpretation. This has been noted especially because: (1) tissues when removed from the body, even under aseptic conditions, tend to undergo autolysis and the products of autolysis are themselves hemolytic, and (2) hemolytic substances have been isolated from fresh normal organs. Robertson [8] found that whereas alcoholic and saline extracts of

5. Queincke: Deutsches Arch. f. klin. Med. **27**:193, 1880.

6. Muir and Dunn, Shaw: J. Path. & Bact. **20**:41, 1915; **21**:417, 1917.

7. Ryffel, J. H.: J. Path. & Bact. **14**:411, 1909.

8. Robertson, O. H.: A Study of Hemolytic Activity of the Spleen in Pernicious Anemia, Arch. Int. Med. **16**:652 (Oct.) 1915; Urobilin in the Stool—Urobilin in the Stool in Pernicious Anemia as Influenced by Splenectomy, Transfusion and Salvarsan, ibid. **16**:429 (Sept.) 1915; An Index to Blood Destruction, **15**:1072 (Dec.) 1915; Robertson and Rous: J. Exper. Med. **25**:665 and 651, 1917.

fresh pulp from spleens removed at operation in cases of pernicious anemia did not possess hemolytic properties, ethereal extracts possessed marked hemolytic activity; ethereal extracts of normal liver and of normal intestine also possessed hemolytic properties. Nolf [9] found that extracts of normal spleen possess marked hemolytic activity, and Banti [10] likewise reported evidence of a hemolytic substance extracted from the spleen. On the other hand, Pearce, Krumbhaar and Frazier [11] reported that they were unable to demonstrate any constant hemolytic properties in saline extracts of fresh spleen, mesenteric lymph nodes or liver.

Wells [11a] said, "It is not generally accepted that the sleep plays an essential rôle in causing pernicious anemia through excessive phagocytosis or production of hemolytic poisons."

It is, however, impossible to deny that because there is no satisfactory evidence of a specific soluble hemolysin that can be isolated from the spleen in pernicious anemia, the spleen does not possess erythrocytocidal properties other than phagocytic. Bottazzi [12] demonstrated an increased resistance of red corpuscles to hypotonic salt solution after splenectomy and suggested that the spleen acts to render the red cells more susceptible to destruction. However, direct proof of this action has not been furnished. Butler [13] studied the resistance of the red corpuscles to hypotonic salt solution in four cases of pernicious anemia and found that they appeared to have normal values. Bigland [14] did not find any abnormal fragility of the corpuscles from six cases of pernicious anemia in which tests against saponin were made, and Rous [15] did not find lowered resistance of corpuscles in cases of pernicious anemia to hemolytic serum. Robertson studied the resistance of red cells taken from the splenic vein and artery in three cases of pernicious anemia in which the spleen was being removed by operation. In each case he found that the cells from the splenic vein showed a distinctly decreased resistance to hypotonic salt solution compared to those taken from the splenic artery. The resistance of the splenic venous corpuscles was less than that of peripheral venous corpuscles and less than that of normal controls. In fact, the resistance of the corpuscles from the peripheral venous blood was greater than normal in most cases. Pearce, Krumbhaar and Frazier [11] stated that the resistance is usually, but not always, increased in pernicious anemia.

9. Nolf, P.: Compt. rend. Soc. de biol. **72**:121, 1912.
10. Banti: Semaine méd. **32**:265, 1912; **32**:313, 1913.
11. Pearce, Krumbhaar and Frazier: Spleen and Anemia, Philadelphia, Lippencott & Company, 1918.
11a. Wells: Chemical Pathology, Philadelphia, W. B. Saunders Company.
12. Bottazzi: Lo Sperimentale **68**:433, 1894.
13. Butler: Quart. J. Med. **6**:145, 1912.
14. Bigland: Quart. J. Med. **7**:370, 1913.
15. Rous, P.: J. Exper. Med. **11**:763, 1909.

In this connection, it should be borne in mind, however, that the reticulated cells may influence the fragility values. Pepper and Peet [16] concluded from their own experiments and from a review of the literature that the reticulated erythrocytes show a greater resistance to hemolytic agents than do unreticulated forms. It would seem from the results of certain observations recorded in this paper that whereas the reticulated cells after hemorrhage are more resistant than the unreticulated forms tested by hypotonic salt solution, those of the reticulated cells of pernicious anemia are less resistant, and if present in sufficiently great quantities may appreciably influence the total fragility so that hemolysis will appear to begin at a higher figure, thus simulating hemolytic jaundice. As Minot [17] pointed out, such cases clinically simulate hemolytic jaundice chronically acquired and are the ones in which the best results are to be expected from treatment by splenectomy.

Of a wholly different nature is the histologic evidence brought forth by Eppinger,[18] who found in the spleens of patients with pernicious anemia hyaline degeneration and increased thickness of the central arteries resulting in a diminution of the caliber of the lumen. As a result of this stenosis, Eppinger concludes that an abnormally great amount of blood is forced directly into the pulp area through the capillaries of Weidenreich. In the pulp area the blood is prepared for hemolysis later to be affected by the Kupffer cells of the liver. The increased destruction of blood in pernicious anemia is thus not due to an increase in the speed with which blood is prepared for destruction.

Schneider stated: "Contrary to the conception of Aldis, hemolysis occurring to the extent of allowing detection of free hemoglobin in the spleen is rare, and whether engulfed by the phagocytic endothelial cells or not, the actual hemolysis occurs in the Kupffer cells of the liver parenchyma. . . Pleiochromia is an expression of immediate hemolysis; urobilinocholia the heaped up pigment in the portal system." Pernicious anemia shows, both Wilbur and Aldis [19] stated, that by means of estimations of urobilin in the urine and feces the forms of anemia associated with increased destruction of blood may be differentiated. Both are high in pernicious anemia.

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16. Pepper, O. H. P., and Peet, N. M.: The Resistance of Reticulated Erythrocytes, Arch. Int. Med. **12**:81 (July) 1913.

17. Minot and Lee: Boston M. & S. J. **177**:761, 1917. Minot, G. R.: Oxford Medicine, vol. 2, p. 589. Lee, R. I., and Minot, G. R.: Cleveland M. J. **16**:65, 1917. Minot, G. R.: Boston M. & J. **174**:667, 1916. Lee, R. I.; Minot, G. R., and Vincent, B.: Splenectomy in Pernicious Anemia; Studies in Bone Marrow Stimulation, J. A. M. A. **67**:719 (Sept. 2) 1916. Minot, G. R.: Bull. Johns Hopkins Hosp. **25**:338, 1914.

18. Eppinger: Berl. klin. Wchnschr. **50**:1509, 1572 and 2409, 1913.

19. Wilber and Aldis: Urobilin: Its Clinical Significance, Arch. Int. Med. **13**:235 (Feb.) 1914.

Further evidence of the mechanical influence of the spleen has been brought forth by Pearce, Hertin and Eisenbrey,[20] who showed that jaundice persisted for a longer period in dogs when hemoglobin was injected into the mesenteric vein than when it was injected into the femoral vein. Warthin [4] has shown that hemolysis by the hemolymph glands exceeds that found in the spleen after splenectomy. Pearce and his collaborators explained the lessened tendency to jaundice after splenectomy as due in part to the fact that the products of red cell destruction are liberated, not into the portal system, but into the general circulation. That such a mechanism may be effective in pernicious anemia is reasonable, but has not been proved.

Finally, the effects of splenectomy in pernicious anemia constitute uncertain evidence, as (1) the results are uncertain, and (2) the hemolymph glands, which are functionally similar to the spleen, may then take on the activities of the spleen. One is inclined to agree with Hirschfield [21] that the spleen is not the essential organ in causing either the excessive phagocytosis or the increased hemolysis in pernicious anemia.

There is little evidence to show that humoral factors may play a rôle in the excessive blood destruction of pernicious anemia. Joannovics and Pick [22] found in experimental phosphorus poisoning an increased amount of unsaturated fatty acids in the serum and suggested that the increased hemolysis may be due to the increased unsaturated fatty acids. Eppinger, and later King,[23] attempted to demonstrate a parallelism between the quantity of unsaturated fatty acids in the serum and the extent of hemolysis in pernicious anemia. McPhedran,[24] however, was unable to demonstrate any undue hemolytic action of unsaturated fatty acid in vitro. In fact, he concluded from his work that "hemolysis by unsaturated fatty acids is not more active in proportion to the degree to which these acids are unsaturated, nor is it diminished when unsaturated carbon atoms are saturated by halogens but is diminished when they are converted into corresponding hydroxyl acids which are hemolytic only to the same degree as saturated acids."

Interesting but unproved is the theory of Cederberg.[25] He conceived of pernicious anemia as a manifestation of anaphylaxis caused by the passage of an incompletely broken-down foreign protein into the circulation through constitutional defects in the intestinal mucosa. This pro-

20. Pearce, R. M., and others: J. Exper. Med. **16**:363 and 780, 1912.

21. Hirschfield: Ztschr. f. klin. Med. **87**:165, 1919.

22. Joannovics, G., and Pick, E. P.: Ztschr. f. exper. Path. u. Therap. **7**:185, 1910.

23. King, J. H.: Studies in the Pathology of the Spleen, Arch. Int. Med. **14**: 145 (Aug.) 1914.

24. McPhedran: J. Exper. Med. **27**:527, 1913.

25. Cederberg: Berl. klin. Wchnschr. **51**:585, 1914.

tein then acts in the blood stream as a hemolytic agent. He reasons from the analogy of observations on the blood of animals dying of anaphylactic shock which shows a certain amount of hemolysis.

TECHNIC OF TEST

Sufficient blood to yield about 25 cc. of serum and 5 cc. of red cells was obtained from the patient and the same amount from a normal person of the same iso-agglutination (isohemolytic) group, determined by the Moss method. All of the patients except two had negative Wassermann tests, and races were not crossed. The Wassermann tests were made in Dr. Mallory's laboratory. The blood specimens from which serums were obtained were placed in large test tubes and allowed to stand in the ice chest until a firm, well retracted clot had formed and the clear serum had separated. The blood specimens from which cells were obtained were defibrinated with beads, centrifugalized and the serum pipetted off, and then washed once with an 0.8 per cent solution of sodium chloride, again centrifugalized, and the supernatant fluid pipetted off. A 50 per cent suspension of these cells was made up in 0.8 per cent salt solution and placed in the ice chest. When the blood in the test tubes had clotted sufficiently well to permit the decantation of the serum, which usually took about four hours, the serum was poured off for use in the test, centrifugalized and the clot discarded. Specimens in which hemolysis had occurred were not used.

The following series of test tubes, each containing 1 cc. of fluid, was then set up in duplicate: (1) salt solution, ranging in concentration from 0.6 per cent, or higher, to 0.1 per cent at intervals of 0.025 per cent; (2) normal serum, two sets, progressively diluted with distilled water, the first tube containing pure serum and each successive tube containing 0.05 cc. more of distilled water and 0.05 cc. less of serum than the one immediately preceding it, until a dilution of serum corresponding to 1:19 was reached; (3) abnormal serum, two sets, diluted in the same manner as the normal serum. To each tube of one of the duplicate sets in each of the three series was then added 0.1 cc. of the 50 per cent suspension of washed normal cells and similarly to each tube of the other of the duplicate sets of each of the three series was added 0.1 cc. of the 50 per cent suspension of the washed cells of the patient. All the tubes were then shaken in order to mix the cells and supernatant fluid and then placed in the icebox for two hours. They were then removed, again shaken, and allowed to stand at the temperature of the laboratory (about 20 C.) for one hour, and then incubated for one hour at 37 C. Observations were then made. In each of the six sets of tubes the dilution at which hemolysis was observed to commence and the dilution at which hemolysis was observed to be complete were noted. Hemolysis was deemed to be complete when the color of the supernatant fluid was of the same intensity as that of a solution of normal red cells made by adding 0.1 cc. of a 50 per cent suspension of such cells to 1 cc. of distilled water. Dilutions of normal and of abnormal serum with distilled water were then made up corresponding to those dilutions at which hemolysis was observed to commence and at which hemolysis was observed to be complete in the case of the normal cells and of the patient's cells. The freezing point depressions of these diluted serums were then determined by means of the Beckmann thermometer in the usual manner. From tables in Landolt and Börnstein's "Compendium," the percentage concentrations of salt solutions corresponding to these freezing point depressions were ascertained. It was deemed more convenient to express all dilutions in terms of equivalent percentage concentration of sodium chloride than in terms of freezing points,

merely because it is conventional to express the results of fragility tests in terms of percentage of concentration of sodium chloride. For this purpose, it is convenient to construct from the standard tables a curve showing the relationship of concentration of sodium chloride to the depression of the freezing point.

A complete record of history, physical observations, laboratory and roentgen-ray reports was made, as all these patients were admitted to the hospital for research. In addition, the following special tests were made: hematocrit, serum color, differential red counts, reticulated red counts, differential white counts, platelets, hemoglobin, color index, coagulation time, bleeding time, blood group—Moss method and Wassermann.

COMMENT

Practically all the tests for fragility of the red blood cells have been made with hypotonic salt solution. A few reports have been made of tests in which saponin and bile have been used. In the composite chart in which the data for abnormal cells in salt solution is shown, the extreme variations for the beginning of hemolysis is 0.51 for hemolytic jaundice and polycythemia to 0.38 for pernicious anemia in remission taken by group. When individual cases are considered, the maximum is 0.65 in a case of undiagnosed anemia (at first thought to be pernicious anemia) to 0.35 in aplastic anemia. These ranges are rather striking when only a few cases are considered, but, when the groups are compared to the normal, which is 0.404, most of the groups appear to have slightly increased fragility for the beginning of hemolysis. The completion of hemolysis in salt solution for the normal is 0.29. while the extremes by groups is 0.27 for pernicious anemia in relapse and septic anemia and 0.19 for polycythemia; in individual cases, 0.35 for pernicious anemia in remission and 0.12 for polycythemia. When the behavior of the cells in salt solution alone is considered, a few cases stand out strikingly, but when groups are considered such definite characteristics cannot be observed, and conclusions cannot be drawn which will make the test of value in diagnosis.

The fragility of the red cells may depend on a number of things:

1. The most fragile cells may have been destroyed in the body before the blood was taken, and when the test is made only the more resistant cells are available.

2. If the severe destruction has taken place several days prior and enough time has elapsed for young cells to be thrown into the circulation in quantities sufficient to influence the test, the resistance of young cells will be tested. Reticulated red cells appear to react normally to salt and serum (chart 1).

3. If the destruction has been gradual over a long period of time and the replacement has appeared at the same rate, a rather wide range of fragility may be found.

4. When the normal rate of destruction has been diminished, the more fragile cells may remain in the circulation for a longer time, and again a wide range of hemolysis may be shown by the hypotonic salt solution test.

So far only the red cells have been considered. This is a single variable and more easily interpreted, but the observations are so close to the normal that undoubtedly the cells are not abnormal to such an extent that they alone can be used for diagnostic purposes. Accordingly, some agent which may with slight changes cause red cell destruction

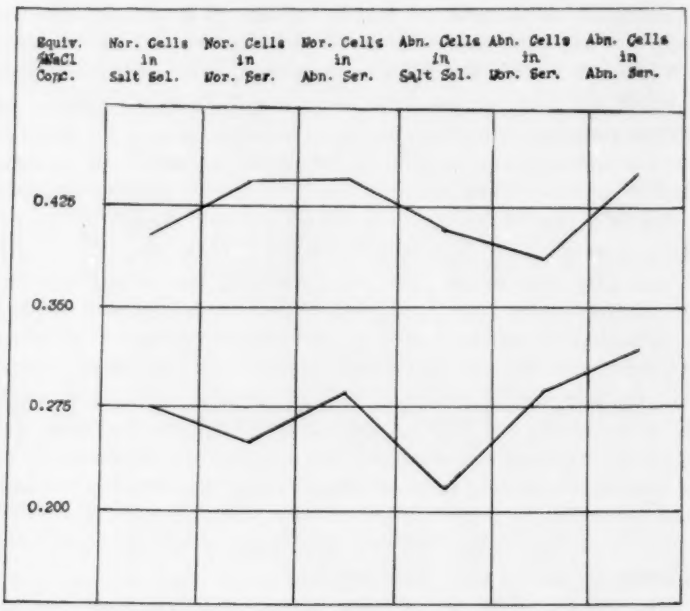

Chart 1.—Reaction of reticulated red cells to hypertonic salt solutions and to normal and abnormal serums. Reticulated red cells, 43.4 per cent; platelets, 254,000; hemoglobin, 30; red cells, 1,200,000, and white cells, 4,000. In each chart the curves are in pairs, the upper curve the beginning of hemolysis, and the lower curve the completion of hemolysis. The space between the two curves represents the range of hemolysis.

or preservation was sought. The different organs of the body and their extracts were studied as described in the first section of this paper. The serum remained uninvestigated.

The serum should produce hemolysis and destruction of the red cell at approximately the same level of salt concentration as the hypotonic salt solution, unless some protective or destructive agent was present.

In order to investigate this principle, seventy-eight normal cases were tested. The beginning of hemolysis was slightly higher in the serums than in the salt solution. It was the same when the cells were put into their original serum or in that obtained from another person. The serums appeared to be protective for the cells, so that the most resistant cells survived in a lesser salt concentration than in the plain sodium chloride. This seems paradoxic. The range of hemolysis for cells in salt was 0.11, while in serum the average was 0.20. This range must be taken into account when the action of a particular serum on red cells is considered. The variation of any normal from the average of the group of normals is very small, so that any marked deviation from the standard normal can be classed as pathologic (chart 2 *A*).

Tests in normal cases in all iso-agglutination groups showed:

(*a*) The mean for beginning hemolysis of cells from normal persons in salt solution is 0.40 for seventy-eight cases.

(*b*) Cells from normal person in own serum 0.45.

(*c*) Cells from normal person in serum of another normal person, 0.44.

(*d*) Greatest difference between "*a*" and "*b*" is 0.10, and 70 per cent of the cases show a difference of less than 5 per cent.

(*e*) Greatest difference between "*a*" and "*c*" is 0.10, and 75 per cent show a difference of less than 5 per cent.

(*f*) Ten of the seventy-eight cases show their own serums less hemolytic than salt solution.

(*g*) One of twenty cases shows other normal serums less hemolytic than salt solution.

Average for Hemorrhage.—A few hours following an acute hemorrhage from trauma, the cells are normal to salt, but the serum is protective to the cells which it contains and to the cells from another person. Perhaps something other than salt has entered the serum which exerts this action or perhaps the cells have adjusted themselves to the newly formed serum. Since the serum protects both its own cells and those from a normal person, it would seem that the serum itself has changed (chart 2 *B*).

Secondary Anemia.—The average for all degrees of secondary anemia is very nearly the same as normal. In individual cases there are striking variations, as in case 68 of early Hodgkin's disease, the abnormal serum is very protective, while in case 76 that of lead poisoning, the serum is destructive both to normal cells and to its own cells (chart 2 *C*).

Hemolytic Jaundice.—The serum reacts normally with normal cells, but some of the cells are more fragile in normal serum and still more so in their own serum, while there are a rather large number of very resistant cells. The lower curve is the same as that in hemorrhage (chart 2 *D*).

Pernicious Anemia—Relapse—Septic Anemia.—This group included all cases in which the diagnosis could be made by the symptoms and observations of the blood at the time the blood was taken for the test. It was in this group that I noticed the marked hemolytic activity of the serum for normal cells and found it necessary to extend the test to include two series of tubes, one for testing the reaction of abnormal cells to normal serum and the second for abnormal cells to abnormal serum. When normal cells are placed in abnormal

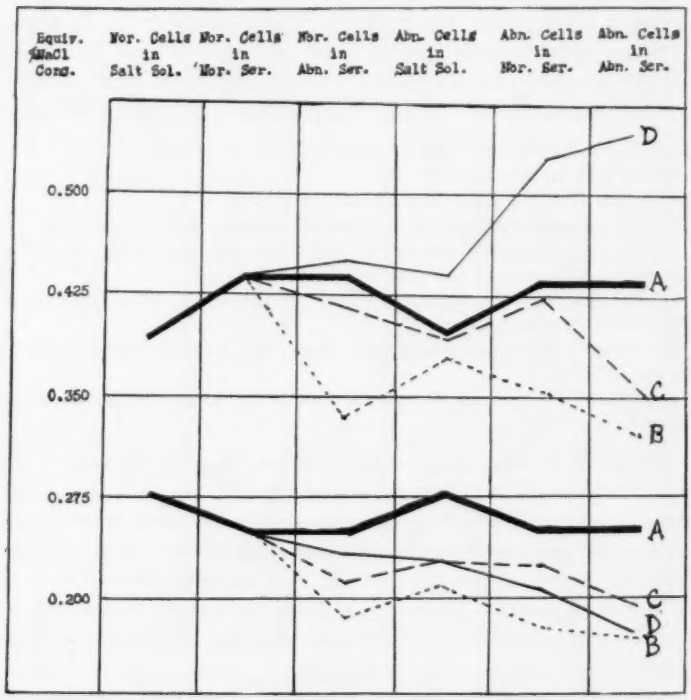

Chart 2.—Range of hemolysis for cells in salt solutions and in normal and abnormal serums. *A* represents the normal average; *B*, the average for acute hemorrhages; *C*, the average for secondary anemia, and *D*, the average for hemolytic jaundice. The lines are in pairs; the upper line indicating the beginning of hemolysis and the lower line the completion of hemolysis.

serum, hemolysis begins at 0.550 (sodium chloride), and when abnormal cells are placed in their own serum, it is increased to 0.58. Many of the cases reach a higher level, as in case 65, to 0.65 and 0.8; case 61, to 0.71 and 0.89. The cells react normally to salt solution. This increased hemolysis in the serum in pernicious anemia is more promi-

nent when the relapse is on the decline and less when on the incline to recovery. In one case it was noticed definitely while the condition was still in remission but just before the relapse which followed in a few days. It would seem from this that some toxic or hemolytic agent is in the serum and that this agent is transitory. If any antibody is formed which causes the remission it is temporary, as a relapse invariably occurs sooner or later. It would be easier to assume that the

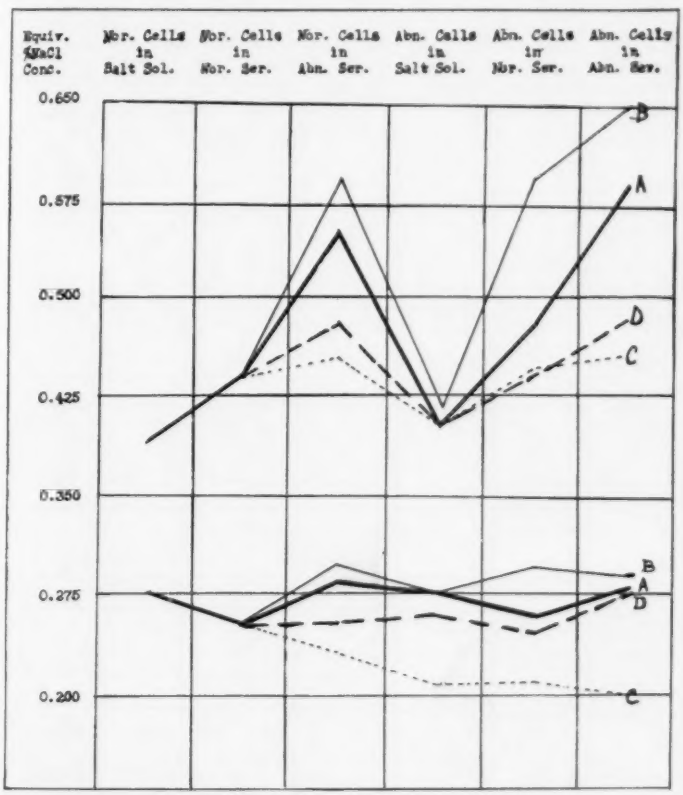

Chart 3.—Curves showing average range of hemolysis at the time of blood test. *A* represents the reaction during the period of relapse of a case of pernicious anemia; *B*, the reaction in septic anemia; *C*, the range for jaundice produced by various causes, and *D*, the period of remission in pernicious anemia.

toxic substance appears intermittently in the blood stream. This curve is almost identical with that of septic anemia. In septic anemia there is an absorption of poisons from a definite focus of infection or abscess. Cases of bacteremia were not included in this group (chart 3 *A* and *D*; also chart 4).

Jaundice.—This group included the various types of jaundice, except the hemolytic. Two cases were syphilitic. The upper curve is normal. The lower is slightly below the normal. The action of bile in the serum on red cells is slight, either on the normal cells or the cells which were in the jaundiced serum (chart 3 *C*).

Pernicious Anemia—Remission.—The curves are normal. The diagnosis had been made previously when the patients were

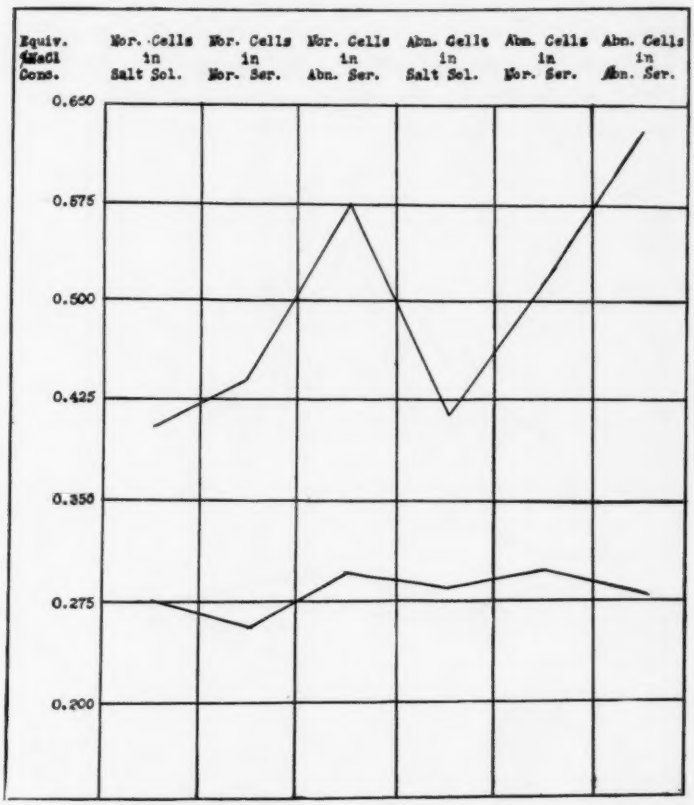

Chart 4.—Curves showing range of hemolysis during the period of relapse in a case of pernicious anemia. Hemoglobin, 30; red cells, 880,000; platelets, 112,000 and white blood cells, 4,000.

in a state of relapse. There were slight variations of the curve for individual cases, depending on which stage of remission they were in, whether just entering it or ready for a relapse (chart 3 *D*).

Polycythemia.—In polycythemia a portion of the cells were very resistant. Many red cells survived a dilution equivalent to sodium

chloride 0.1, determined by microscopic examination. Some of the cells were slightly more fragile than normal. An interesting question can be raised here as to the cause of polycythemia. The cells may increase in number because they are exceedingly resistant and defy the normal destruction mechanism while the rate of production continues the same.

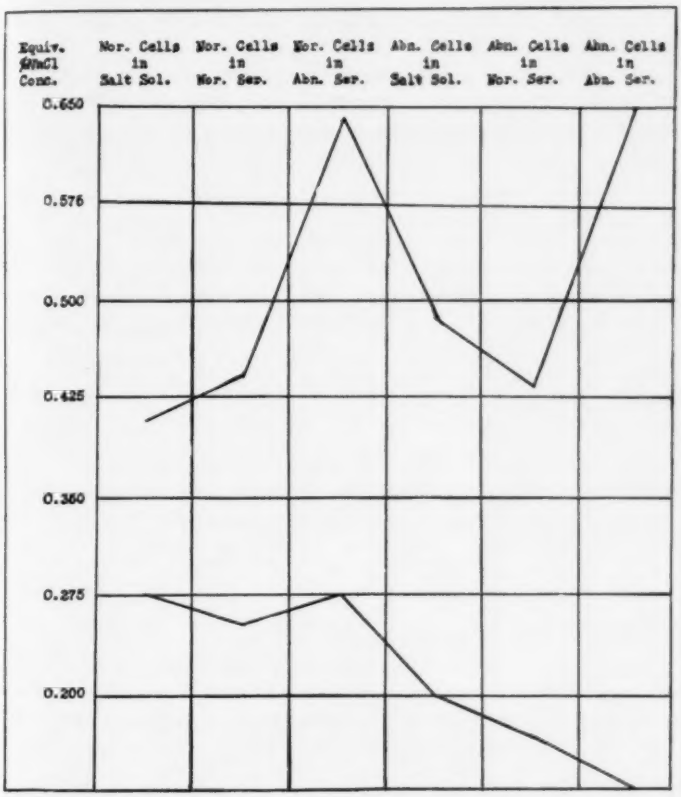

Chart 5.—Averages in polycythaemia serums; hemoglobin, 140; red cells, 8,620,000; platelets, 260,000, and reticulated red cells, 2 per cent.

Unclassified.—This includes a variety of cases of known diagnosis and some doubtful.

SUMMARY OF CASES

In case 4, the patient had a severe anemia and presented some of the symptoms and signs of pernicious anemia and aplastic anemia, also symptoms of hemolytic jaundice at times. Transfusion was used a

number of times, with temporary relief. This test proved that the red cells were at times extremely fragile, being hemolyzed in normal serum with a sodium chloride concentration of 0.89 and her own serum 0.884. The serum was not hemolytic to normal red cells. In case 70, one of trichinosis, the blood serum was normal. In case 28 which was not diagnosed, the cells were extremely fragile. In case 5, hypertrophic cirrhosis of the liver with severe jaundice, the serum was hemolytic. In case 40, aplastic anemia, the cells were resistant: nevertheless it was necessary to give the patient transfusions every thirty to

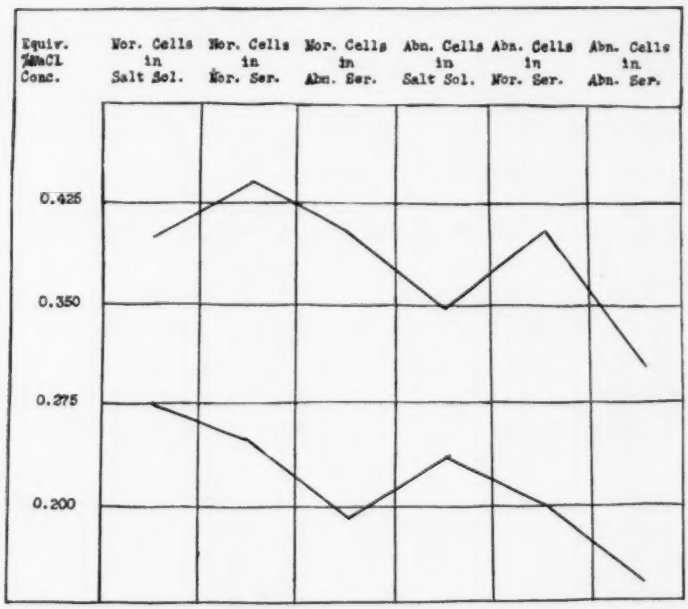

Chart 6.—Averages in reaction of cells in aplastic anemia; hemoglobin, 25.7; red cells, 1,310,000; white cells, 4,200; platelets, 192,000; serum deeply yellow.

forty days. He felt well in the intervals and did his usual office work (chart 6; also table 2).

CONCLUSIONS

1. Under certain conditions there are hemolytic substances in the blood serum. The unknown substances act in vitro and may also act in the blood stream on the red cells.

2. Blood serum in patients with pernicious anemia who are having relapse contains a hemolytic substance for its own red cells and also for normal red cells.

TABLE 1.—*Characteristic Features of Diseases Studied as Shown by Mean Values in Abnormal Cases*

Minimal Hemolysis Concentration	Hemorrhage	Aplastic Anemia	Secondary Anemia	Hemolytic Jaundice	Pernicious Anemia	Polycythemia
Col. 3	N	—	N	+	N	+
Col. 4	—	N	N	+	N	+
Col. 5	—	N	—	—	+	+
Col. 6	—	—	—	+	+	+
Span						
Col. 3	+	—	N	+	N	+
Col. 4	+	—	N	+	N	+
Col. 5	N	N	—	—	+	+
Col. 6	N	—	—	+	+	+

Span indicates difference between minimal and complete hemolysis concentration; N, value within normal range; +, value greater than normal maximum; —, value less than normal minimum. Col. refers to the column in the charts.

TABLE 2.—*Fractions of Cases Showing Extra Normal Values*

Minimal Hemolysis Concentration	Hemorrhage		Aplastic Anemia		Secondary Anemia		Hemolytic Jaundice		Pernicious Anemia		Polycythemia	
	+	—	+	—	+	—	+	—	+	—	+	—
Col. 3	0	2/6	0	2/2	0	0	2/2	0	2/20	6/20	2/4	0
Col. 4	0	5/6	0	0	0	3/20	2/2	0	4/20	0	3/4	0
Col. 5	0	5/6	0	0	2/20	13/20	0	2/2	17/20	0	3/4	0
Col. 6	0	5/6	0	2/2	0	6/20	2/2	0	17/20	0	4/4	0
Span												
Col. 3	3/6	0	0	2/2	3/20	0	2/2	0	2/20	5/20	3/4	0
Col. 4	4/6	0	0	2/2	4/20	0	2/2	0	5/20	1/20	4/4	0
Col. 5	0	1/6	0	0	6/20	8/20	0	1/2	13/20	0	2/4	2/4
Col. 6	0	1/6	0	2/2	2/20	9/20	2/2	0	14/20	0	4/4	0

The numerator refers to the number of cases showing extra normal values; the denominator refers to the number of cases of the disease studied.

TABLE 3.—*Percentage in 110 Cases Studied Showing All of the Deviations from the Normal by Mean Values Including Certain Cases of Slight Deviation from the Normal Obliterated or Only Vaguely Represented in Mean Values*

Hemorrhagic	Aplastic Anemia	Secondary Anemia	Hemolytic Jaundice	Pernicious Anemia	Polycythemia
50%	100%	40%	50%	60%	50%

TABLE 4.—*Percentage of Cases Other Than Disease in Question Showing All Characteristics of Mean Values for that Disease Without Abnormalities*

Hemorrhage	Aplastic Anemia	Secondary Anemia	Hemolytic Jaundice	Pernicious Anemia	Polycythemia
3%	1%	2%	1%	9%	0

3. Serum in hemolytic jaundice and septic anemia also contains a hemolytic substance.

4. The red cells are abnormal in polycythemia, aplastic anemia and secondary anemia.

5. Reticulated red cells of normal size are more resistant than the nonreticulated.

6. This test is of value in the differential diagnosis of anemia and for determining the resistance of the red cells and the hemolytic power of the serum.

547 West Jackson Boulevard.

A RECORD SYSTEM SUITABLE FOR BOTH CLINICAL AND STATISTICAL MEDICINE*

HALBERT L. DUNN, M.D.
AND
REED ROCKWOOD, M.D.
BALTIMORE

Notation of clinical observations has existed since the beginning of medicine. A large portion of the present knowledge of disease has come from the summation of the bedside notes made by the physician. Before the occurrence of comparatively recent scientific trends in modern laboratory medicine, the clinical record might well have been considered as the corner-stone on which all medical knowledge was built.

In the past three decades the basic medical sciences have advanced with tremendous strides. The microscope and the test tube have yielded scientific facts of utmost importance. The knowledge obtained from observation made at the bedside has progressed with the advance in laboratory medicine but has scarcely kept pace with it. This is due, in part at least, to the ignorance displayed by the clinical group in modern statistical technic. The analysis of clinical records, which is the scientific proving ground for clinical observation, has been carried on in an inadequate fashion. The reason for the failure to use the statistical science may be assigned largely to the form of the clinical record which does not yield itself to technical analysis. Modern tabulating technics are available which, if applied to the problem, should fulfil the demands of statistical medicine, permit extensive analysis of clinical facts and consequently furnish a yardstick for clinical procedures

Only one essential difference exists between the demands of statistical medicine and those of clinical medicine. Statistical technic demands completeness of negative as well as of positive information for all items of sufficient importance to be considered a part of the disease syndrome. In clinical medicine completeness is interpreted in terms of positive facts about the case, but notation of the bulk of negative observations is ignored. The laws of probability cannot be applied unless the true

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* The death of Dr. Reed Rockwood occurred after this article was accepted for publication. The loss of his scientific interest and zealous cooperation in laboratory and clinical research problems is keenly felt by his co-workers.

probabilities are known. If all the negative observations are not present, these true probabilities cannot be calculated.

In the writing of the history and physical examination as it is carried on at the present time, practical difficulties arise to prevent the satisfactory notation of negative observations. The physician cannot and will not take the time to write a list of negative answers; consequently it is almost hopeless to expect complete notation in the history and physical examination as it is done today.

On the other hand, many valuable features of the clinical chart in its present form must not be sacrificed for the completeness so desirable in any numerical analysis. The ideal record for both clinical and statistical medicine must be individualistic and personal in character. Questions in the history must be asked in the proper sequence. The notation of negative data should be so facilitated that it does not add a burden to the duties of the physician. The record should be sufficiently elastic to meet all demands put on it, and it should yield information readily. A single glance at the clinical record should suffice for the consultant to locate the particular item in which he is interested while he is standing by the bedside of his patient.

During the last year we have developed a chart for general history and physical examination (fig. 1) which seems to fill the needs of both clinical and statistical medicine. The chart has been filled out for the hypothetical diabetic record of Mrs. H. Brown, and this case will be used for illustrative purposes throughout the paper. The chart has been devised with a view of conserving the physician's time and effort and at the same time of obtaining a far more complete set of clinical data concerning the general case. It has had the advantage of rather widespread general criticism and of detailed scrutiny from a number of physicians. When possible, every feasible suggestion was worked into the chart.

We do not expect that this record will prove satisfactory in all types of institutions. In all probability, it will be too extensive for physicians to use in their private practice or for dispensary services. We are at present working on an abridgment suitable for both the private physician and the dispensary. The present chart was devised for the record of the patient in a hospital on the average hospital service. The questions and notations represent our idea of a minimal requirement for a reasonably complete routine clinical record in a hospital.

The form does not represent a complete system of records. There are many medical specialties such as eye, ear, nose and throat, dentistry, obstetrics, psychiatry, neurology, dermatology and others which are inadequately represented by this chart. The general history and physical

examination is intended to be the hub in a wheel of medical records. The records of specialties will dovetail into this general chart without overlapping; consequently, the items in the chart are always in the form of leading questions and leading physical observations which, if positive, will suggest a special, more detailed examination.

It is important to note that the use of this chart does not curtail any type of history or physical examination in use at present. There is sufficient writing space to expand the data whenever it is desirable. In case insufficient blank space is allotted in the booklet, blank sheets may be inserted at any place; in fact it is considered highly desirable to expand the routine questions and notations. Good records can be obtained only by amplification of positive answers and observations.

The entire first sheet of the history is occupied with routine facts customarily demanded in all histories. If a specific institution has its own diagnosis sheet, it is not necessary to use the few lines allotted on this chart for that purpose; otherwise the diagnoses are listed in this space.

The present illness is to be noted in chronologic order. The routine questions of the past and present illness (fig. 1, pp. 4 and 5) have been printed in the words which a physician uses in talking to his patient. Whenever possible the necessity for definition of medical terms was avoided, since the phrasing of questions differently by various physicians would undoubtedly elicit a variety of answers from the patient.

There are only three ways in which a given question can be checked. The check mark means positive, the zero means negative and a question mark signifies unknown. If a question is left blank, it is considered to be unasked. Unasked questions defeat the purpose of the chart, which is to gain completeness. In certain places, the brackets list subquestions which do not have to be asked; for example, under the respiratory system (fig. 1, p. 4), if the patient said he did not have tonsillitis or sore throat, it would be unnecessary to ask about the frequency of attacks. If the answers to the questions in an entire section should be negative, one zero written on the main section heading would indicate that the questions under all subheadings had been asked and the answers found to be negative. For example, the genito-urinary system (fig. 1, p. 5) is indicated in this manner. If the answers for any column of questions are negative, a zero can be written after the first and last question, and a straight line drawn between the zeros to show that those for all intervening items are likewise negative. For example, under respiratory system (fig. 1, p. 4) all answers between nosebleed and night sweats inclusive are indicated to be answered in the negative in this manner. By means of these short cuts, negative notations are reduced to a minimum.

After each system, in both the history and physical examination, the physician is requested to interpret the symptoms of the entire section in view of what significance these symptoms mean to him at the moment. For instance, a number of observations on the heart were checked (fig. 1, p. 11), and the summary reads: "Heart moderately enlarged, functional murmur."

The routine facts of the history are placed on page 6. The notation of the family, marital and menstrual history and of habits is self-explanatory. Degrees 1, 2 and 3 signify mild, moderate and excessive, respectively. Definition of the limitations of these degrees will not be attempted. They are qualitative measures and will be used as such. The specific institution or physician using the chart may define degree as desired.

The last section in the history represents somewhat of an innovation. It is well recognized that histories are not of the same quality or statistical value; consequently, the physician is requested to grade the history after he has finished writing it. For example, in the record of Mrs. H. Brown, this section is marked zero, which indicates a satisfactory history.

The first page in the section on physical examination calls for the routine measurement of height and weight which is customary in most medical services at the present time. If the patient is too sick to obtain his weight on admittance, this measure may be filled in at a later date and the date noted in parenthesis. Surface area is a computed constant and does not need to be recorded unless it is desired by the specific institution.

If the notation of an intern is checked by a consultant, it is possible for the latter to recheck the same chart with a different colored writing fluid. When differences between the notes of the consultant and intern exist, the notes of the consultant should be accepted by the record department.

Several lines are allowed for the general description of the patient. A considerable group of internists consider that such a statement is more important than any other item in the physical examination. A terse description is requested which will be sufficiently accurate so that a visiting physician can select the patient among many others. It forces the examiner to observe the patient as an individual.

Two pages are left for description of the principal abnormalities in the words of the examiner. It would be ridiculous to assume, for example, that the checking of the routine observations on the heart would give a good picture of a disturbance of the heart. A graphic detailed description of such an abnormality is indispensable. In the

illustrated diabetic case of Mrs. H. Brown, it was not necessary to describe in detail any of the summarized principal abnormalities (fig 1, p. 7).

Before writing the results of the routine physical observations, the physician will examine his patient from head to foot in the customary manner. He will then sit down to check the chart. All of the items listed are abnormalities; consequently, even if the physician does not have certain specific points in mind when he examines the patient, he recognizes the absence of such abnormalities. He is able to scan the list, and frequently to answer entire sections without referring to the patient. In case he overlooks the observation of a few items, it is reasonable to expect him to recheck these points.

As in the history, zero indicates a negative answer, a check mark a positive one, and a question mark, doubtful observations; there should not be any blanks or unanswered items. Degrees are noted as 1, 2 and 3, indicating mild, moderate and excessive, respectively.

The location of abnormalities in the spine, lungs, heart, abdomen, extremities and skin is required. The location of symptoms of the spine and skin is accomplished by a cross line drawn from the symptoms to the involved parts. In the case of disease of the lungs, heart, abdomen and extremities, the location of symptoms is obtained by a line drawn from the symptoms to the diagram. For example, the location of râles (fig. 1, p. 10) is noted on the diagram by a line from both bases posteriorly to the type of râles found in this location.

The clinical value of mensuration of the heart is a debatable question. It was only after considerable discussion with heart specialists that a decision was made to require a measurement of the right and left border of cardiac dulness at the level of the second rib and apex. These measurements can be made in centimeters by the scale printed on the edge of the sheet. A sketch of the outline of the heart is desirable but cannot be expected as a routine notation. Accentuation and diminution of the heart sounds and heart murmurs must be located in respect to the aortic, pulmonic, mitral or tricuspid areas.

Under neurologic observations, the degrees 1, 2 and 3 have been extended to the negative side of normal, and signify diminished, moderately diminished and absent reflexes, respectively.

The term "sensitive achilles' tendon" needs explanation. Libman has shown that by deep, steady pressure over the styloid processes and by noting the response of the patient, he has a rough measure of the reaction of the patient to unpleasant sensations. This reaction forms an excellent guide to the evaluation of the symptoms concerning which the patient complains. The response can be controlled by pressure over the mastoid bone which is not normally unpleasant.

1

No. 67,190 GENERAL HISTORY Date Sept. 1, 1927

Examiner: Harris Consultant: Rockwood (use different color ink or pencil) Race: USA Color: W. B.

Patient's Name Mrs. Harold Brown Address 213 W. 22nd St., City

Age: 42 Sex: M. ✓ F.—Civil State: S. M. W. D. Sep.—Occupation Hw.

Referred by Dr. F.A.Logan Address 2414 N. Charles St.

Responsible Relative Husband Address above

Previous Admissions None

Final Diagnosis: Date September 5th, 1927

Diabetes mellitus. Arteriosclerosis general. Hypertension. Diabetic acidosis. Chronic constipation. Hemorrhoids. Obesity

Outcome Improved.

Recommendation

Binding Margin

Chief Complaint Weakness

Present Illness (Chronological Order)

Loss of Weight: Amount 30 lbs.; Duration 1 yr.

Loss of Strength: Degree 1, 2, 3, Cot; Duration 1 yrs.

Last Date When Patient Was Well Fall, 1926 Date Onset of Symptoms Aug. 1927

Date

1926 Patient was last perfectly well about a year ago. At this time she began to notice a little loss in weight altho her appetite was still rather good. She began to notice that she could not do her housework as well as formerly and would seem to tire more easily. This sensation of weakness gradually became progressively worse. She also noted that she would be dizzy on sudden change of position of the head, such as on getting up suddenly or out of a chair or on getting up in the morning.

Aug. 1927 During this month she noted a headache on rising nearly every morning fronto-occipital in type, which wore away during the course of the day. This was relieved to some extent by taking Salicylic acid.

2

Date

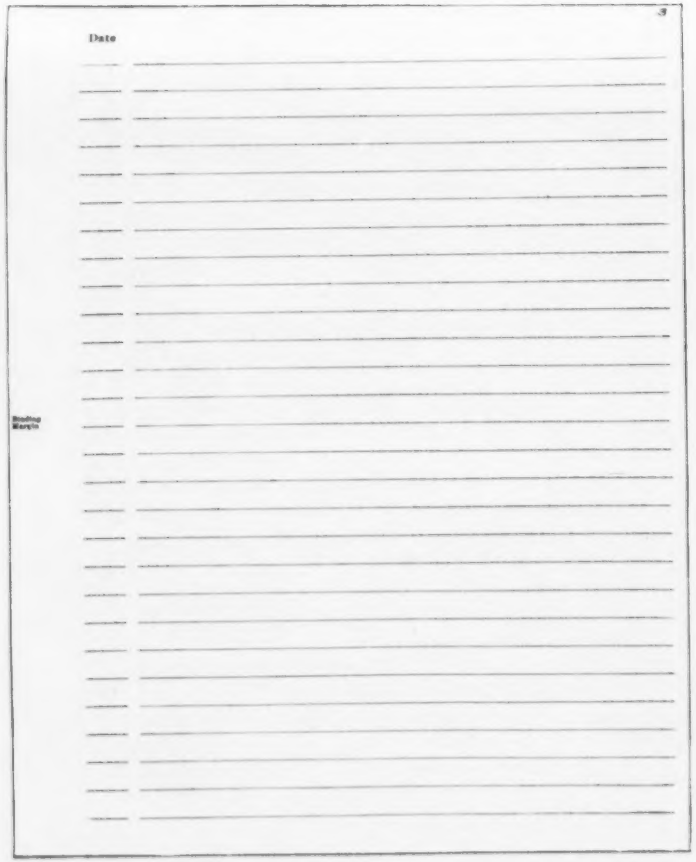
Aug. 15th The patient caught cold in the head bout this time and went to bed a day or two because of prostration and general aches and pains all over. She was able to get up and around the house again, but has little residual cough, and since this time has never felt well. At this time she noted that she was drinking large quantities of water and passing large quantities of urine. She had to get up 2 - 3 times a night which she had never previously done.

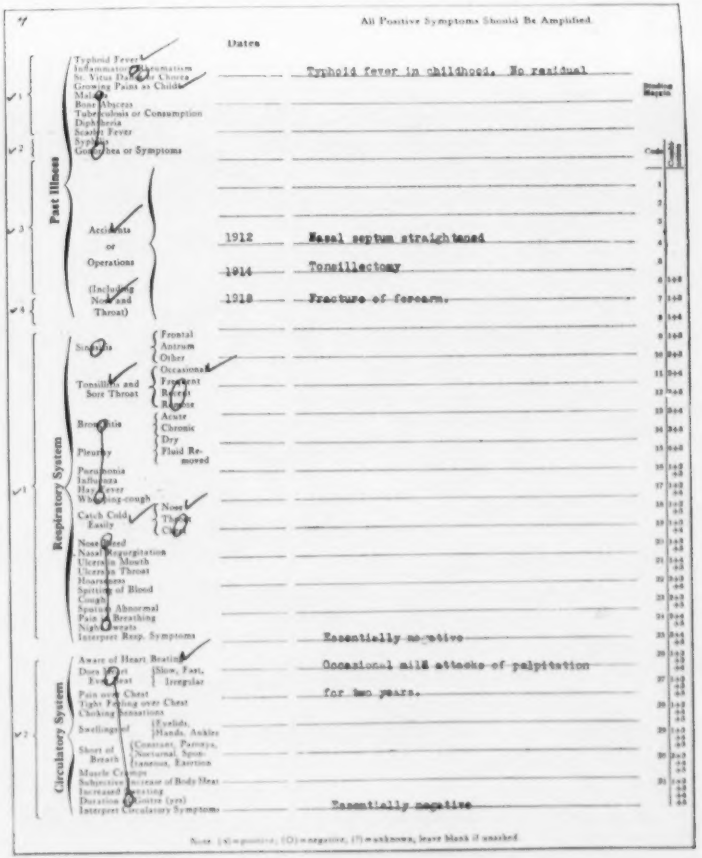
For the last few days she has felt very tired and exhausted and has stayed in bed most of the time. She aches all over and still has a little cough.

Binding Margin

Fig. 1.—Form for recording general history and results of physical examination. This form is used as a twelve page (six leaf) booklet, 8½ by 11 inches in size. It is filled out with the illustrative case record of Mrs. H. H. Brown.

Fig. 3.—Form for recording general history and results of physical examination. This form is used as a twelve page (six leaf) booklet, 8½ by 11 inches in size. It is filled out with the illustrative case record of Mrs. H. H. Brown.





All Positive Symptoms Should Be Amplified. 5

Dates

Gastro-Intestinal System

Appetite; Below, Normal, Above
Water; Below, Normal, Above
Trouble Swallowing
Abdominal Pain (Locate) — Mild, Moderate, Severe; Duration
Indigestion — Belching; Bloating; Vomiting (Food, Blood, Bile, Retention); Heartburn; Soda Relief
Jaundice
Bowel Movements — Bow. Mov. No. 0-1; Cathartics (How Often, Kind); Attacks of Constipation; Attacks of Diarrhea; Pain on Defecation
Hemorrhoids
Stool — Pus, Blood, Clay, Tarry, Incontinence
Interpret G. I. Symptoms

For 20 years bowels have only moved every day or two with cathartic pills or salts 2 - 3 x a week.

Occasional attacks of protruding hemorrhoids.

Chronic constipation and hemorrhoids

Genito-Urinary System

Frequency (Day, Night)
Burning or Smarting
Pain
Slow Starting
Slow Stopping
Retention
Incontinence
Interpret G. U. Symptoms

Negative

Nervous System

Sense of Equilibration
Subjective Nervousness
Hours of Sleep, No. 6-9
Headaches
Head Injury
Paralysis
Fainting Spells
Fits or Convulsions
Unsteady Gait
Tremor
Loss of Voice
Tingling or Numbness in (Hands, Feet)
Dizziness
Aches or Pains in (Muscles, Joints)
Loss in Sexual Power
Mental Conflicts — (Business, Financial, Family Affairs, Sexual, Health, Religious)
Special Senses — Ear (Ache in Childhood, Discharge, Deafness, Ringing); Eye (Pain, Light Sensitive, Sees Double, Inflamed Lids, Vision Failing, Has Worn Glasses yrs, Duration Exophthalmos yrs.)
Interpret Ner. System Symptoms

See present illness

See present illness

Negative except for headaches and vertigo.

Note: (✓)=positive; (O)=negative; (?)=unknown, leave blank if unasked

Weight Curve (Pounds): At 20 125 At 30 140 At 40 160 At ___ At ___ Max. 198 1926 Min. 80#

Family History

	Father	Paternal ♂	Paternal ♀	Paternal Aunts	Paternal Uncles	Mother	Maternal ♂	Maternal ♀	Maternal Aunts	Maternal Uncles
Tuberculosis or Consumption										
Cardio-Renal (Apoplexy, Stroke; Kidney, Bladder or Bright's; High Blood Pressure; Heart Trouble)	✓									
Sick Headaches										
Convulsions										
Epilepsy										
Nervous Trouble										
Mental Trouble										
Cancer										
Diabetes	✓									
Tendency to Bleed Easily										
Other Illness Similar to Patient's										

Mother and maternal G.M. obese

Marital History

First Mate Dead or Sick, Cause
Second Mate Dead or Sick, Cause
Third Mate Dead or Sick, Cause
Years Present Marriage 34 Mate Living and Well ✓

Children in Birth Order	Living and Well	Abortion	Miscarriage	Born Dead	Died: Age	Died: Cause
1.	✓					
2.						
3.						
4.						
5.						
6.						
7.						
8.						

Menstrual History

Began At Age 14
Regular (Days) 28
Irregular (Days)
Duration (Days) 5
Menorrhagia: Degree- 1, 2, 3
Metrorrhagia: Degree- 1, 2, 3
Pain (Degree- 1, 2, 3; Time of - Before, First Day, During)
Leucorrhea: Degree- 1, 2, 3
Date of Last Period 1925 ✓

Habits

Alcohol: Degree- 1, 2, 3
Drugs: Degree- 1, 2, 3
Coffee: Degree- 1, 2, 3
Tea: Degree- 1, 2, 3
Tobacco: Degree- 1, 2, 3
Other Harmful
Grade at School 12

History is Inaccurate, Very Poor, or No Good Due To —

Language Difficulty
Antagonism to Examiner
Poor Power of Expression
Secretive of Sexual Life
Secretive of Venereal History
Mentally Inferior
Extreme Youth or Old Age
Indifference
Extreme Illness
Extreme Pain
History Given by Relative or Friend (Adequate, Inadequate)

Note: (✓)=positive; (O)=negative; (?)=unknown, leave blank if unasked. Degrees 1, 2, 3=mild, moderate and excessive

No. 67,190 PHYSICAL EXAMINATION Date Sept. 1, 1927

Patient's Name Mrs. Harold Brown Examiner: Harris Consultant: Rockwood
(use different color ink or pencil)

Height (in. or cm.) 5'4" Weight (lbs.) 160 Surface Area (sq. m.)

Temp.(Mouth, Rectal) 98.4
(Abnormal)

General Description of Patient.

Somewhat obese, elderly, gray-haired woman lying in bed.
Seems a little dull mentally.

Detailed Summary of Principal Abnormalities

1. Retinitis
2. Dehydration
3. Non-toxic adenoma
4. Rales at bases
5. Cardiac hypertrophy
6. Hypertension
7. Hemorrhoids
8. Peripheral arteriosclerosis
9. Toxemia
10. Obesity

Binding Margin

Binding Margin

All Positive Findings Should Be Amplified

Head and Face

- Hair: Alopecia; Moth Eaten
- Shape: Hydrocephalus; Enlarged Face Bones
- Eyes: Lids (Ptosis; Inflammation); Arcus Senilis; Movements (Strabismus; Nystagmus; Exophthalmos); Pupils — Reaction To: Accommodation (Absent; Partial); Light (Absent; Partial); Irregular; Right > = < Left; Miosis; Mydriasis; Blindness (Partial; Complete); Abnormal Fundi (Disc; Vessels; Hemorrhages; Exudates; Scars)
- Ears: Tinnitus; Deafness (To Whisper; To Loud Voice; Total); Discharge (Serous Type; Pus; Blood)
- Nose: Obstruction to Breathing; Abnormal Shape (Saddle; Fractured; Bridge Enlarged)
- Jaw: Swellings: Upper, Lower; Deformities: Upper, Lower

Interpret Head and Face Findings

Vessels a little narrowed and tortuous in right eye near disc; at 3 o'clock is a group of three small white spots of exudate

Mild retinitis. Arcus senilis

Mouth and Throat

Lips Abnormal—How?

- Gums: (Metallic Line; Pyorrhea)
- Teeth: (Amount of dentistry: 1, 2, 3; Caries—Degree: 1, 2, 3; Hutchinson's)
- Mouth: (Coated; Swollen; Atrophied)
- Tongue: (Dry; Deviates to Right or Left; Tremor)
- Palate: (Cleft; Ulcerated)
- Pharynx: (Inflamed; Membrane; Ulcerated)
- Tonsils: In—Antiseptic; Out—O. K.; Out—Antiseptic Tag; Size: (Enlarged; Pus Expressed; Large Tonsillar Nodes; Inflamed Ant. Pillars)
- Larynx: (Aphonia; Hoarseness)

Interpret Mouth and Throat Findings

Tongue very dry and coated

Negative except dehydration

Note: (X)=positive; (O)=negative; (/)=unknown; leave blank if not noted

All Positive Findings Should Be Amplified

Neck

- Cervical Lymph Nodes (Enlarged; Tender)
- Stiffness
- Abnormal Pulsation (Venous; Arterial)
- Thyroid: Enlarged (Diffuse; Nodular); Consistency (Soft; Medium; Hard); Tenderness (Right > = < Left; Both)

Interpret Neck Findings

3 cm. nodules in right lobe of thyroid

Spine

- Kyphosis; Lordosis; Scoliosis; Limited Motion; Tenderness; Percussion — (Cervical; Thoracic; Lumbar; Sacral; Sacro-Iliac; Kidney Area) Locate by Cross Line

Interpret Spine Findings

Non-toxic adenoma

Thorax

- General Respiratory: Cough; Sputum (Purulent, Mucous, Mucopurulent, Watery, Tenacious, Fetid, Bloody, Rusty)
- Mass in Breast: Size (cm.); Tenderness; Connects with Skin; Examiner's Impression (Benign; Malignant; Questionable)
- Dyspnea (Inspiratory; Expiratory)
- Cheyne Stokes Respiration; Paroxysmal Respiration
- Inspection: Type of Chest & Costal Angle (Describe); Deformities of Chest (Emphysematous; Rachitic; Unilateral)

Interpret Thorax Findings

Negative

Anterior Chest

Right Left

Posterior Chest (Locate Findings By Cross-Lines to Physician)

Left Right

Chest and Lungs

- Inspection: Ribs (Retracted; Bulging); Interspaces; Abnormal Respiratory Movement (Unequal; Descent Limited; Limited Ant. or Post.)
- Tactile Fremitus
- Percussion (Hyperresonance; Dull; Flat)
- Auscultation: Abnormal Breath Sounds (Vesicular, Broncho-Vesicular, Tubular; Diminished, Absent); Abnormal Whispered Voice (Very Loud, Increased; Diminished, Absent); Abnormal Spoken Voice (Very Loud, Increased; Diminished, Absent); Rales (Moist; Crepitant; Mucous); Friction Rub

Interpret Chest and Lung Findings

A few moist rales at the bases

Passive congestion

Note: (X)=positive; (O)=negative; (/)=unknown; leave blank if not noted

All Positive Findings Should Be Amplified

Heart

Inspection: Dilated — Vessels; Neck, Arm, Chest; Abnormal Pulsations; Bulgings

Palpation: Localize Apex; Shock: Sys. Diastolic; Thrill: Sys. Dias. Presys.

Percussion: Outline Abnormal

Auscultation: Aortic 2nd — Pul. 2nd; Accentuation: A P M T; Diminution: 1st 2nd A P M T; Murmurs: Sys. Dias. A P M T; Pres.; Murmurs: Transmitted; Abnormal Rhythm

Rate of Heart: 84 (At Apex) 84 (Radial)

Abnormal Rhythm

Vessels

Blood Pressure: 198 Sys. 110 Dias. (Indicate: Position, Standing, Sitting, Recumbent)

Arterio-Sclerosis: Type, Radial, Brachial

Interpret Circulatory Findings

— Heart outline normal

(Measure Diameters, Draw Outline and Indicate Findings By Cross Line)

— X —

Heart moderately enlarged. Functional murmur

Abdomen

Inspection: Peristalsis; Distension; Dilated Vessels; Operative Scars

Palpation: Tender: General, Local; 1,2,3; Rigid: General, Local; 1,2,3; Fluid Wave

Organs: Liver Edge; Spleen; Uterus; Kidney (Enlarged, Movable); Bladder; Colon; Gall Bladder

Mass: In Abdominal Wall (Ing. Hernia, Fem. Hernia, Ventral Hernia); Intra-Abdomen (Locate, Describe, Movable, Fixed)

Inguinal Rings Relaxed

Interpret Abdominal Findings

Right Left (Indicate Findings By Cross Line to Diagram)

Negative

Extremities

Club Digits; Fracture; Edema; Varicosities; Varicose Ulcer

Motor: Atrophy; Hypertrophy; Spasm; Fibrillation; Paralysis; Tremor

Joints: Ankylosis; Crepitation; Dislocation; Effusion; Fixed In; Locomotor Ataxia; Pain; Tenderness; Swelling; Motion Inhibited

Interpret Extremity Findings

(Locate Findings By Cross Lines to Diagram)

Negative

All Positive Findings Should Be Amplified

Neurological

Knee Jerk; Ankle Jerk; Tuning Fork; Sensitive Tendo-Achilles: -3 -2 -1 Normal +1 +2 +3

Gait Abnormality; Positive Romberg; Speech Abnormal; Interpret Neurological Findings

Lymph Nodes

Cervical: Enlarged, Tender; Axillary: Enlarged, Tender; Epitrochlear: Enlarged, Tender; Inguinal: Enlarged, Tender

Skin

General: Acne; Anidrosis; Hyperidrosis; Cyanosis; Jaundice; Pallor; Pigmentation; Petechiae; Edema; Eruption; Inflammation — Generalized; Trunk; Upper Extremities; Lower Extremities; Nails; Scalp; Face and Neck; M. M. of Mouth; Conjunctiva; Genitalia

Local (Locate Findings By Cross Lines)

Dry skin

Interpret Lymph Node and Skin Findings

Genitalia

M: Lesion; Scar; Tumor; Phimosis; Testicular Atrophy; External Genitalia Abnormal

F: Virgin; Married; Postpartum

Bi-Manual: Uterus (Retroverted, Prolapsed); Mass (Cervical, Pelvic)

Rectum and Anus

Mucosa: High, Low; Smooth, Irregular; Blood on Finger; Movable, Fixed

Prostate Enlarged; Seminal Vesicles Enlarged; Fissure; Fistula; Hemorrhoids; Diminished Pouch; Sphincter Ani

Interpret Genito-Rectal Findings

Few small external tags

Abnormal Psyche

Disoriented; Lacks Attention; Poor Memory (Last Week, Past Life); Mood: Depression, Elation; Sensorium Clouded; Restlessness; Delusions and Hallucinations; Comprehension: Excellent, Good, Poor, None, Neg.; Intelligence: Excellent, Good, Average, Moron, Defective

Toxemia

Interpret Psychic Findings

Primary Impression

Diabetes mellitus. Diabetic acidosis

Note: (+)=positive; (-)=negative; (?)=unknown; leave blank if not asked.

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Note: Basis 3; 1 = slight, 2 = moderate, 3 = extreme.

LABORATORY AND SPECIAL EXAMINATIONS

(Code: 1) — Urine

Date		9/1	9/2	9/3		
Hours		55	12	24		
Amount			350	940		
Specific Gravity		1018	1010	1012		
Reaction		ac	ac	ac		
Albumin	Basis 3	T	T-H	0		
	Grams					
Sugar	Basis 3	3+	3	3		
	Grams		25.0	28.0		
Acetone		3+	3+	2+		
Diacetic		3+	0	0		
Bile						
Urobilin Bodies						
Hemoglobin						
Centrifuged — Casts	Hyaline	occ				
	Granular	occ	occ	occ		
	Cellular					
Non-centrifuged	R. B. C. (3)	0	0	0		
	Pus (3)	T	T	occ		
	Micro. Neg.					
Cath. or Uncath.		Cath	Cath	Cath	C.U.	C.U.
Residual if Cath. (cc.)						
Tubercle Bac.						
Miscellaneous						

(Code: 1) — Blood Chemistry

Date		9/1	9/2	9/3		
Non-Protein Nitrogen		46		37		
Urea						
Uric Acid						
Creatinine						
Sugar		368	225	230		
Chlorides						
CO_2 Vol. %		15	41			
Miscellaneous						

(Code: 2) = Hb. to WBC; 3 = Pl. to Comment

— Blood Examination —

Date		9/2				
Hb. (gms. or %)		58				
R. B. C. (mil.)		67				
Color Index						
W. B. C. (Thousands)		11.0				
Platelets (Thousands)						
Bleeding Time						
Coagulation Time						
Blood Smear and Differential — No. Cells Counted						
Lymphocyte %						
Large Mono. %						
Transitional %						
Neutrophile %						
Eosinophile %						
Basophile %						
Anisocytosis						
Poikilocytosis						
Bas. Stippling						
Polychrom'ia						
Malaria						

Miscellaneous & Comment

(Code: 4) — Wassermann — Date: 9/2 — Negative

(Code: 4) — Spinal Fluid — Date:

(Code: 3) — Sputum — Date:

(Code: 3) — Throat Culture — Date:

(Code: 3) — Blood Culture — Date:

(Code: 5) — Widal — Date:

(Code: 2) Basal Metabolic Rate — Date:

(Code: 2) Electrocardiograph — Date:

(Code: 3) Cystoscopic — Date:

(Code: 4) Stool — Date: 9/3 — Neg for parasites & occult blood

(Code: 4) Proctoscopic — Date:

(Code: 4) Fractional Test Meal No. 1

Interval Hrs							
Total Acid							
Free H C							
Quantity cc.							

Food Remnant, Blood, Total cc: _____

Miscellaneous

(Code: 4) Fractional Test Meal No. 2

Interval Hrs.							
Total Acid							
Free H C l							
Quantity cc.							

Food Remnant, Blood, Total cc: _____

Miscellaneous

(Code: 3) — Phthalein Test

Date	1 V %	1 M %	Residual Urine cc.
9/3		45	

Page 1

—X-RAY EXAMINATIONS—

Date:

Code: 1 Head, Neck and Thorax; 2 Skeleton, Extremities, Spine and Pelvis; 3 Gastro-Intestinal Tract; 4 Abdominal Viscera, Urinary System and Misc.

9/3 Chest neg. except for slight cardiac hypertrophy

9/3 Right frontal sinus blurred

(Code: 3) —DENTAL EXAMINATION—

Examined by SG Date 9/4

Right: 1 2 3 4 5 6 7 8 — 32 31 30 29 28 27 26 25

Upper: 9 10 11 12 13 14 15 16 — Left: 24 23 22 21 20 19 18 17

Lower

Periapical Infection: No. 31-26-3 Degree II

Pyorrhea: No. 4-5-21-20 Degree III Impacted or Unerupted: No. 0 Operate: Yes, No

Remarks:

(Code: 3) —EAR, NOSE, THROAT—

Examined by PC Date 9/4

Diathermy Margin

Right frontal opaque to transillumination. Pus II in Nose

Tonsils non septic

(Code: 1) —EYE EXAMINATION—

Examined by OTO Date 9/4 Vision 20/20 R.L. Pupils O.K.

Reflexes O.K. Fields

Fundi Moderate arterio sclerosis with a little exudate in right.

MISCELLANEOUS LABORATORY TESTS AND REPORTS

Code: 3 Tests A-L Done but Normal; 3 Tests A-L Done Abnormal; 4 Tests M-Z Done but Normal; 5 Tests M-Z Done Abnormal

Give Dates:

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Page 2

Fig. 2.—Loose-leaf laboratory sheet printed on both sides. It is filled out with [illegible]

Patients may show varying grades of hypersensitiveness and hyposensitiveness. One of us has tried this test and believes that it is important, but that for the average patient it is better elicited by firmly squeezing the achilles' tendon. The amount of reaction on the part of the patient is then noted on the chart by the numbers 1, 2 and 3 on the positive or negative side of normal.

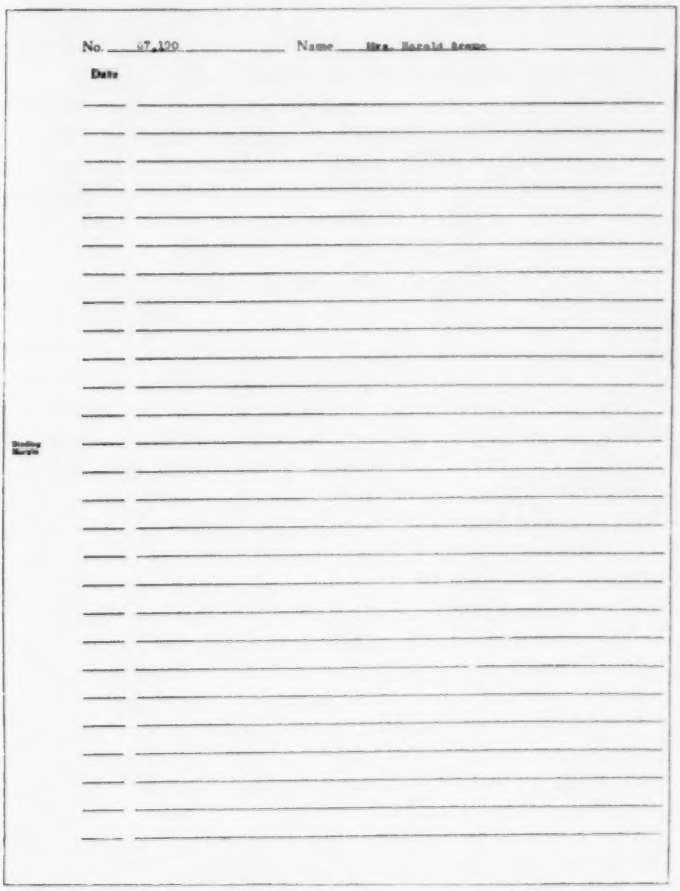

Fig. 3.—Loose-leaf supplementary blank sheet, printed on both sides.

The primary impression represents a summary of the observations, both history and physical, after the first examination of the patient has been completed.

It will be noted that the chart has been copyrighted in the names of Dunn and Rockwood; this was done solely to protect it from com-

mercialization, and permission will be granted freely for any physician or medical institution to reprint it for professional purposes.

The laboratory sheet (fig. 2) is original in construction but not in content. It does not demand special description. It was formulated primarily with the intention of incorporating the cross-index feature, to be discussed later, into laboratory observations.

The blank sheet (fig. 3) can be used to fill in for additional space at any part of the record.

The physical form of the chart has been planned with the following specifications:

1. The general history and physical examination are bound and printed together in the form of a twelve page booklet. This booklet can be printed with binding margin at either the side or the end of the chart, as desired. The order of the sheets is the same whether the pages turn as in a book, or whether they are bound so as to open lengthwise.

2. The laboratory and blank sheets are printed on both sides as detached papers.

3. The entire form will be on letter-size paper, 8½ by 11 inches, which is the size suitable for the standard files of all hospitals.

4. In order to obtain the maximum efficiency in the mechanical handling of these charts, it is essential to have a unit number for each patient, and it is desirable to keep all records of the patient in a unit file rather than in a bound volume.

5. The lines throughout the chart are so spaced that double or triple space on all standard makes of typewriters will allow the type and printed lines to coincide.

6. The cheapest quality of paper which can be used is a 24 pound basic ledger substance. This paper is not regarded by paper manufacturers as permanent since it has a low percentage of rag in its composition. It is a better grade, however, than most of the paper used in the majority of hospitals at the present time. To demand a more permanent paper would raise the entire question of the length of time which hospital records should be kept—a discussion beyond the scope of this publication.

7. The testing of this chart is now in progress at six hospitals. It is also being tried out by a number of physicians in their private practice. In this trial the chart will be subjected to actual working conditions. If it is possible to obtain completeness in the notation of all the required facts in the majority of cases without interference or handicap to the clinical routine, the chart will be considered successful. There are many questions which must be answered before the material in these records can be analyzed with a maximum degree of efficiency.

The variation between observations of physicians with different degrees of medical experience; the variation in answers due to questions being purely subjective or objective in character; the variation in a given patient in his reaction to different physicians, in his answers under various diseases or mental conditions; and the variation of the patient on successive examinations; these and kindred questions must be answered before the reliability of the facts in the chart can be determined.

The points in favor of this form for recording the results of general history and physical examination may be summarized as follows:

1. It is just as individualistic as the types used by physicians at the present time for recording the history and the results of physical examinations. It sacrifices none of the sequence in disease events and none of the personal elements existing between the patient and the physician.

2. The chart definitely facilitates the notation of clinical facts.

3. It yields information much more readily than the present forms in common use because a given fact is located in a specified section.

4. The accuracy of the record depends entirely on the competency of the physician. The element of forgetfulness on the part of the examiner is practically obviated.

5. The chart will be more legible than if it were entirely in handwriting.

6. The record of the case is sufficiently elastic to meet most demands in modern medicine. In case a given institution has a great many patients of a certain type, it may be necessary to amplify this general form with a special printed sheet, giving the specific questions and observations desired, as, for example, one suitable for the record of a patient with diabetes, cardiac or dermatologic conditions.

7. The record will be far more complete in respect to negative information than any existing type.

8. It should prove to be a considerable aid in the training of students. It will facilitate the orderly arrangement of their clinical ideas, and will point the way to the art of history taking, which involves the following up of leading questions and observations.

9. It will afford an opportunity for one to measure the variability in recorded facts due to the personal equation of the examiner or of the patient.

10. It will furnish adequate statistical material for the clinician interested in the analysis of disease entities.

11. With all of these advantages, the time of recording the history and physical observations is reduced, as compared with present records of equivalent value.

12. The adoption of a record form of this general type is essential if the physicians in a hospital hope to obtain an adequate cross-index of the contents of their records.

The technical features of the cross-index will now be considered in detail.

DESCRIPTION OF MECHANICAL CROSS-INDEX

A mechanical cross-index scheme has been worked out for the clinical record just described. It may or may not be used, as desired. An attempt will not be made in this article to describe the numerous systems of cross-index which are in use at the present time in hospitals throughout the country. After a careful consideration of modern methods of tabulation, the mechanical punch-card system was selected as the best available tool to bring about a solution to the problems in the cross-indexing of hospital records.

Raymond Pearl first suggested the adaptation of a mechanical punch-card as a medical index method. A detailed description of his plan is given in the original article.[1]

Although the system proposed by Pearl has an enormous advantage over any other developed in the past, owing to its elasticity and the mechanical handling of information, certain difficulties arise in the practical application of his plan:

1. The use of multiple secondary cards complicates the index.

2. Multiple entries in the history and physical observations are frequently a desirable feature in the search for records.

3. The entire index is kept up in the form of a number of punch-cards in each case. As records pile up in numbers, mechanical sorting, rapid as it is, will become a considerable chore when tens or hundreds of thousands of cards are manipulated. Moreover, punch-cards kept too long a time will wear out, become swollen from dampness and will jam in the machine.

4. The adaptation of the index plan depends on the rental of tabulating machinery by all hospitals, the expense of which most small hospitals would find prohibitive.

Before describing the index system which we propose in connection with this record, it is desirable to list the needs which should be fulfilled by an ideal cross-index for hospitals. The essential features are as follows:

1. The index should show the location of the record of any case desired by the physician within as brief a time as possible.

2. It should prevent the misplacement of records owing to multiple or ambiguous diagnoses.

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1. Pearl, Raymond: Modern Methods in Handling Hospital Statistics, Bull. Johns Hopkins Hosp. **32**:184, 1921.

3. It should permit the location of records by the history, physical and laboratory observations, as well as by diagnoses.

4. It should fill the needs of a small hospital with about the same efficiency that it does a larger one.

5. It should be adequate for departments of hospitals engaged in specialized branches of medicine.

6. It should be simple technically, in order to be kept by ordinary clerical help.

7. It must be economical.

Without checking over the good or bad points of any particular system, it would be generally admitted by physicians who have analyzed clinical records that, at the present time, the existing methods of cross-index do not measure up to all the features in the ideal system just enumerated.

A description of the cross-index used in this chart may be divided into seven parts:

1. Description of a punch-card for general purposes.

2. Description of the specially printed punch-card used in the proposed index.

3. Description of the codes used in the index which are as follows: code for diagnosis; for age; for sex and color; for outcome of case and civil state; for history; for height; for weight; for physical examination; for laboratory observations, and for miscellaneous items of interest.

4. Description of the technic of punching cards and what it means to the record department of the average hospital.

5. Description of the printed cross-index.

6. Estimation of the cost of a mechanical index system.

7. Summary of arguments for the mechanical cross-index.

DESCRIPTION OF A PUNCH-CARD FOR GENERAL PURPOSES

A punch-card for general purposes is shown in figure 4. This card is 7⅜ by 3¼ inches in size. It is printed by both the Powers Accounting Machine Corporation and the International Time Recording Company, which are the two principal competitors in this field. Holes have been punched in this card by a machine which will be described later. There are forty-five columns of numbers on the card. Each column runs from zero to nine in value. The small numbers at the bottom of the card represent the number of the column and are never punched. Any one of the numbers from zero to nine can be punched in any one of the forty-five columns.

Ordinarily, only one number is punched in a given column. Although there are only ten numbers printed in any given column, there are twelve possible positions that may be punched. The eleventh position (also called the X position) has been punched in column 15. The twelfth position (also called the blank position) has been punched in

column 14. It is customary, but not essential, to reserve the twelfth position for unknown or negative information. For instance, if column 14 had been coded for racial distinctions and the twelfth position was punched, it would mean that the item of race had not been noted in that particular patient.

Occasionally it is desirable to punch two holes in the same column as demonstrated in columns from 30 to 34. This double punch complicates sorting and printing of the cards, but is permissible in certain instances as will be shown subsequently. In referring throughout the remainder of the description of this cross-index to any code division on the card, the column number will be given and then the punch number in the column; for instance, in figure 4, various items would

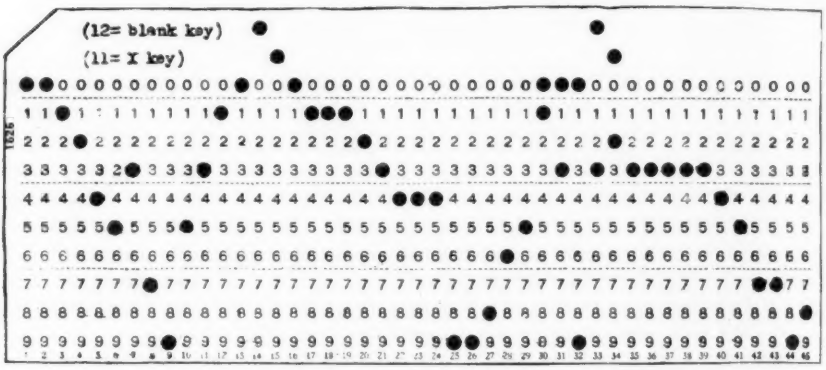

Fig. 4.—Punch card for general purposes.

be read as column 8, no. 7; column 14, no. blank; column 15, no. X; column 30, nos. 0 and 1; column 33, nos. blank and 3; column 34, nos. X and 2; and so on.

DESCRIPTION OF THE SPECIALLY PRINTED PUNCH-CARD USED IN THE PROPOSED INDEX

The blank card illustrated in figure 4 can be printed and designed to fit any desired purpose of tabulation. Figure 5 represents the punch-card printed for the proposed mechanical cross-index. Figure 6 represents the same card which has been punched to represent the coded information found in the illustrative chart of Mrs. H. Brown noted in figure 1. The first six columns indicate the case number of the chart. Case number 1 would be punched as 000001 in columns 1, 2, 3, 4, 5 and 6, respectively. The record number of Mrs. H. Brown, 67190 is punched as 067190 in the first six columns. The highest

number which can be recorded is 999999 and allows, therefore, for a tabulation of that many separate patients.

Columns from 7 to 21 are set aside for diagnoses. Three columns, 7, 8 and 9, are allotted for the first diagnosis and two columns each are allowed for the remaining diagnoses. The first column in each diagnostic field, namely, 7, 10, 12, 14, 16, 18, and 20 can be double-punched.[2] In each of these first columns the blank position represents 1, the X position 2, and the zero position 3 in units of 10. It is possible by this means to indicate forty numbers in one column. The number zero will be indicated if a hole is not punched in the column, and numbers from 1 to 9 if the printed numbers from 1 to 9 are punched. If the blank position is punched, it will signify code no. 10. The numbers from 11 to 19 will be indicated by a double punch, namely, the blank position for the 1 in units of 10 and the proper unit number

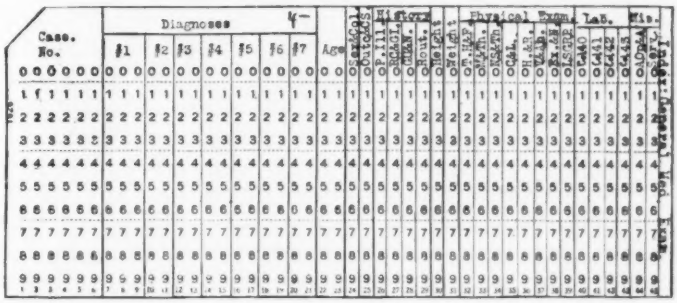

Fig. 5.—Punch card printed as an index card for the general medical examination.

from 1 to 9; no. 20 by a single punch in the X position which represents 2 in units of 10; nos. 21 to 29 by a double punch, one of which is the X position representing 2 in units of 10 and the other the proper unit number from 1 to 9; no. 30 by a single punch in the zero position which stands for 3 in units of 10 and numbers from 31 to 39 by a double punch, one of which is the zero position representing 3 in units of 10 and the other the proper unit number from 1 to 9.

The second column in each diagnostic field is punched in one position only. Eleven positions may be indicated in this column which are, respectively, the blank position, 0, 1, 2, 3, 4, 5, 6, 7, 8 and 9. It is possible, therefore, to code into hundreds in each two-column field for any given diagnosis. The numbers would read serially as 00-blank,

2. In order to accord with the wiring possibilities of the printing tabulator only twenty-five columns can be double-punched. We have taken advantage of every one of these possibilities in the proposed cross-index card.

000, 001, 002, 003, 004, 005, 006, 007, 008, 009, 01-blank, 010, 011, 012, etc., up to the highest number which would be 399. Counting the blanks and zeros as separate numbers, this code permits the division of each diagnostic field into forty major headings in the first column with a subdivision of each of these into eleven subsidiary units in the second column. The total number of items which it is possible to list in the two-column field by this process is 440.

A survey made in several hospitals shows that usually in about 80 per cent of the case records there is only one diagnosis. Multiple diagnoses up to four are fairly common, and over seven extremely unusual. The first diagnosis, columns 7, 8 and 9 has a third column, no. 9, which permits the subdivision of each of the 440 items in the first two columns into eleven subsidiary units allowing for 4,840 items in the code of the first primary diagnosis.

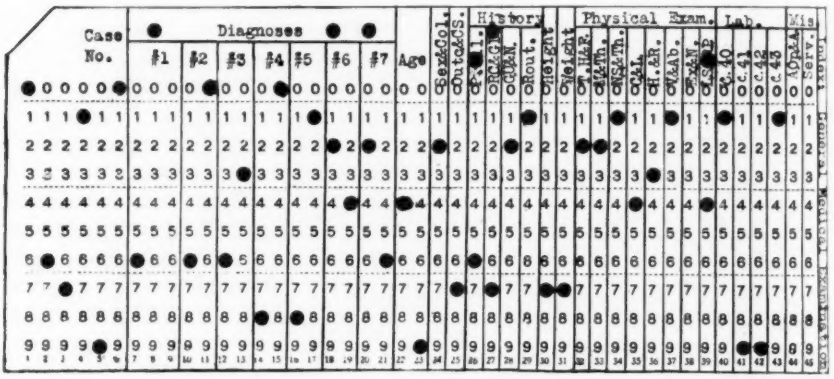

Fig. 6.—An index card for the general medical examination, which has been punched for the illustrative diabetic record of Mrs. H. Brown, noted in figures 1 and 2.

If there should be multiple diagnoses of eight or more numbers for any given hospital record, the code number of these diagnoses should be written in ink on the back of the card. Any card which has been punched for seven diagnoses must be examined for written code numbers on the back. It is estimated that this event should not occur more than once in two or three hundred times.

In the record of Mrs. H. Brown, illustrated in figure 1, there are seven diagnoses. These diagnoses with their respective code numbers are as follows: (1) diabetes-mellitus (6 blank); (2) obesity (60); (3) diabetic acidosis (63); (4) general arteriosclerosis (80); (5) hypertension (81); (6) chronic constipation (124), and (7) hemorrhoids (126).

The diagnostic code has not been filled out to thousands and, consequently, the third column in the first diagnosis is left unpunched. The code number of diagnosis 1 (6 blank) is punched in columns 7 and 8; that of diagnosis 2 (60) in columns 10 and 11; of 3 (63) in columns 12 and 13; of 4 (80) in columns 14 and 15; of 5 (81) in columns 16 and 17; of 6 (124) in columns 18 and 19, and of 7 (126) in columns 20 and 21.

The next four columns of the punch-card from 22 to 25 represent the items of age, sex, color, outcome and civil state. Age is coded in columns 22 and 23; sex (male or female) and color (white or black) in column 24; outcome (well, improved, same, worse or dead) and civil state (single, married, widowed, divorced or separated) in column 25. For example, the age of Mrs. H. Brown (fig. 6) is indicated as 49 in columns 22 and 23, the sex (female) and color (white) are coded as no. 2 in column 24, and civil state married and outcome improved by code no. 7 in column 25.

The main divisions of the history occupy four columns from 26 to 29; each is double-punched, using the blank key as 1, the X key as 2 and the zero key as 3 in units of ten. By this means, numbers up to forty can be indicated in the same manner as described for the first column of each diagnostic field. Column 26 represents past illnesses including abnormalities in the weight curve (fig. 1, p. 6); 27, the respiratory, circulatory and gastro-intestinal systems; 28, the genito-urinary and nervous system; and column 29, the routine history and the clinician's opinion of the accuracy of the history.

Only thirty-one numbers of the possible forty are used in each one of these columns. Each of the thirty-one numbers represents an abnormality or combination of abnormalities. It is possible to list five separate items or any combination of these five items by use of the combination code printed on the history (fig. 1, p. 4). The past illness, for instance, is divided into five subdivisions. If any one of the diseases from typhoid to scarlet fever has been checked in the past illness, no 1 is marked as positive. If the patient has had syphilis, gonorrhea or a history of abnormal weight curve (p. 6),[3] no. 2 is checked; if he has had a major operation or accident, no. 3; a nose or throat operation, no. 4; and if there is some important item in the miscellaneous, not included in the routine list of past illnesses, no. 5 is checked.

3. The code position of the weight curve is placed with past illnesses, while its chart position naturally falls after the routine question by systems. It represents the only divergence in the arrangement by order between the index code and the printed chart.

If the patient has only one of these five conditions, for instance no. 2, the coded number would be identical to the number checked on the chart. If, however, he had items 1, 2 and 4 checked, this combination would be indicated by code no. 17 in column 26 of the index card.

In figure 1 code no. 26 is punched in column 26 representing positive observations in the past illness in items 1, 2, 3 and 4. Likewise, code no. 17 in column 27 represents positive observations in items 1, 2 and 4.

Body height, grouped by classes, is given in column 30, and body weight, also by classes, in column 31. Mrs. H. Brown has a stature of 64 inches (162.56 cm.) represented by code no. 7 in column 30, and a body weight of 160 pounds (74.4 kg.) indicated by code no. 7 in column 31.

The physical examination occupies eight columns, from 32 to 39, each one of which is double-punched, so that it can represent numbers up to 40. All of the code numbers in the physical examination stand for abnormalities. In column 32, abnormalities of the head and face are noted; 33, of the mouth and throat; in 34, of the neck, spine and thorax; in 35, of the chest and lungs; in 36, of the heart; in 37, of the vessels and abdomen; in 38, of the extremities and neurologic symptoms and 39, of the lymph nodes, skin, genitalia, rectum and abnormal psyche.

Abnormal laboratory observations are indicated in columns 40 to 43.

Columns 44 and 45 have been set aside for miscellaneous conditions and may be assigned in any way desired by a specific institution. We suggest a certain arrangement which may or may not be followed. In this arrangement, four conditions are coded in column 44 which might exist in any diagnosis or any case, namely, autopsy, major operations, minor operations and previous admissions. This leaves a fifth blank space for some special interest still unassigned. Column 45 could be reserved for the indication of the principal service on which the patient was treated. Many hospitals would not desire to make such a distinction between their records.

DESCRIPTION OF CODES USED IN THE INDEX

Code for Diagnosis.—Various codes for diagnoses, particularly the international code of death and the morbidity code used by the United States Navy, were scrutinized with a view to molding them into a code for diagnosis to be used in hospitals. We found all of these codes undesirable for general use in a hospital; the principal objection to them is that they have been formulated in a fixed, inelastic manner. The purpose of the diagnostic code for hospital use is to facilitate the location of records. The coding of diagnoses to a degree of minutiae that involves the recording of isolated individual cases will defeat the essential purpose of the code, namely, speed in the search for required

records. The code must be elastic if it is to fill the needs of various types of institutions. For example, a hospital for the treatment of patients with a disease of the eye will need a complete code for observations on the eye, and nothing but the major headings in most of the other groups. The tuberculosis sanatorium will need detailed questions on the diagnosis of the chest and the obstetric department a special amplification on obstetric complications.

The code for diagnosis represents a skeleton outline on which any institution may build its respective diagnostic interests. Each item which has been entered in the outline, both major headings and subdivisions, has been selected after a survey of numerous hospital reports, and entered in the code only if a widespread occurrence of that particular diagnosis exists and if it represents a significant proportion of the total number of patients treated in a hospital.

It is to be noted that there are six major divisions in this code which have been left unassigned so that any institution may indicate as a major interest some unusual local activity. Likewise, there are two or three unassigned subdivisions under each major division. It is important to note, also, that the last major heading is reserved as a miscellaneous group for those diagnoses which do not fit in any of the other groups. The last subdivision under each one of the major headings is reserved as a miscellaneous section. A good rule to follow in the development of a practical code for diagnosis is always to keep the miscellaneous groups below 5 per cent of the total number in its particular section. If some element causes the miscellaneous column to mount above this 5 per cent limit, it should be separated from the miscellaneous group and placed in the code as a separate element

The code for diagnosis, therefore, is only an outline around which a particular selection of items should be arranged which will best suit the needs of the institution using the code.

Code for Diagnosis

0 blank to 29 Communicable diseases (except 3 blank to 49)

0 (blank)	Diphtheria
00	Dysentery (including all forms of amebiasis)
01	Erysipelas
02	Fevers of unknown origin
03	Gonococcus infections
04	Influenza
05	Malaria
06	Measles
07	Mumps
08	Mycoses (diseases caused by fungi)
09	Parasites and parasitic insects (diseases due to, including scales, pediculosis, chiggers and others)

10 Protozoa (diseases due to, with the exception of malaria, amebiasis and syphilis)
11 Pertussis
12 Pneumococcus infections and other pneumonias
13 Rheumatic fever
14 Septicemia
15 Typhoid fever
16 Diseases of the upper respiratory tract
17 Varicella
18 Variola
19 Vincent's angina
20-28 Blank
29 Miscellaneous

3 blank to 39 Syphilis
3 (blank) Diagnosis by serology and otherwise not clinical
30 Early infections
31 Late infections of central nervous system
32 Late infections of vascular system
33 Late infections of skin and mucous membranes
34 Late infections, visceral
35 Congenital infections
36-38 Blank
39 Miscellaneous

4 blank to 49 Tuberculosis
4 (blank) Pulmonary
40 Bone and joints
41 Lymphatic system
42 Gastro-intestinal tract and peritoneum
43 Genito-urinary system, both male and female.
44 Skin and mucous membranes
45-48 Blank
49 Miscellaneous

5 blank to 59 Neoplasms
5 (blank) Benign growths
50 Carcinomas of gastro-intestinal tract
51 Carcinomas of female reproductive organs (including breast)
52 Carcinomas of skin and mucous membranes
53 Miscellaneous carcinomas
54 Sarcomas
55 Other types of malignant tumors
56 Tumors the type or malignancy of which is in question
57-58 Blank
59 Miscellaneous

6 blank to 69 Metabolic and deficiency diseases
6 (blank) Diabetes mellitus
60 Obesity
61 Undernutrition (including starvation)
62 Dietary deficiencies (including rickets)
63 Acidosis and alkalosis
64-68 Blank
69 Miscellaneous

7 blank to 79 Diseases of blood and blood forming organs (except 3 blank to 59)

7 (blank) Anemia (including primary, secondary, hemorrhage and others)
70 Leukemias and Hodgkins
71 Purpura and hemorrhagic diseases of the new-born
72 Splenomegalies
73 Abnormal constituents of blood used as diagnoses
74-78 Blank
79 Miscellaneous

8 blank to 89 Diseases of vascular and lymphatic system (except 3 blank to 59)

8 (blank) Aneurism and aortitis
80 Arteriosclerosis and senility (except 240)
81 Hypertension and hypotension
82 Phlebitis, thrombosis and varicosities
83 All other diseases of arteries
84 All other diseases of veins
85 Diseases of lymphatic system (including lymph nodes and thymus)
86 Vasomotor and trophic disturbances
87-88 Blank
89 Miscellaneous

9 blank to 99 Diseases of heart (except 13, 14, 3 blank to 59, 21 blank, 211 and 27 blank)

9 (blank) Diseases of myocardium (including myocarditis, myocardial insufficiency, cardiac pain and others)
90 Diseases of pericardium (including pericarditis, adherent pericardium)
91 Diseases of endocardium (including endocarditis, valvular lesions, acute and chronic)
92 Cardiac failure from any cause
93 Arrhythmias
94 Cardiac neuroses and neurocirculatory asthenia
95-98 Blank
99 Miscellaneous

10 blank to 109 Diseases of nose, throat, mouth and pharynx (except 0 blank, 04, 06, 07, 11, 16, 19, 3 blank to 59 and 27 blank)

10 (blank) Diseases of nose and accessory sinuses
100 Diseases of tonsil and adenoid tissue
101 Dental, gingival conditions and lips
102 Diseases of tongue, salivary glands and palate
103 Diseases of pharynx
104-108 Blank
109 Miscellaneous

11 blank to 119 Diseases of esophagus, stomach and duodenum (except 3 blank 59 and 27 blank)

11 (blank) Diseases of esophagus, stomach and duodenum
110 Abnormal stomach contents including observations on acidity
111 Peptic ulcer
112 Functional dyspepsias of all types
113 Other diseases of stomach
114 Other diseases of duodenum
115-118 Blank
119 Miscellaneous

12 blank to 139 Diseases of intestines, colon, rectum, anus, peritoneum and abdominal viscera (except 00, 09, 10, 15, 3 blank to 59 and 27 blank)

- 12 (blank) Appendicitis (acute and chronic)
- 120 Obstruction and perforation (including ileus)
- 121 Enterocolitis (acute and chronic)
- 122 Diseases of peritoneum
- 123 Ascites and adhesions
- 124 Constipation
- 125 Diarrhea
- 126 Local rectal and anal conditions (including fistulae, fissures and hemorrhoids)
- 127 Diseases of gallbladder and biliary tract (including cholecystitis and cholelithiasis)
- 128 Diseases of liver
- 129 Jaundice
- 130 Diseases of pancreas (except 6 blank)
- 131 Diseases of spleen (except 72)
- 132-138 Blank
- 139 Miscellaneous

14 blank to 149 Diseases of respiratory system (except 0 blank, 04, 11, 12, 16, 19, 3 blank to 59)

- 14 (blank) Diseases of larynx
- 140 Diseases of bronchi (such as bronchitis, bronchiectasis)
- 141 Bronchial asthma and hay-fever
- 142 Foreign bodies
- 143 Diseases of pleura (such as pleurisy, thickened pleura and empyema)
- 144 Other diseases of lungs
- 145-148 Blank
- 149 Miscellaneous

15 blank to 169 Diseases of urinary tract (except 03, 3 blank to 59 and 27 blank)

- 15 (blank) Nephritis
- 150 Uremia
- 151 Pyelitis and pyelonephritis (including hydronephrosis and stricture)
- 152 Cystitis
- 153 Other infections and fistulae in urinary tract (including perinephritic abscess)
- 154 Abnormalities of urine used as diagnosis
- 155 Disturbances in flow of urine (such as enuresis, anuria)
- 156 Other disturbances of kidney
- 157 Other disturbances of ureter
- 158 Other disturbances of bladder
- 159 Other disturbances of urethra (except gonorrhea)
- 16 (blank) Postoperative conditions
- 160-168 Blank
- 169 Miscellaneous

17 blank to 179 Diseases of male reproductive system (except 03, 3 blank to 59 and 27 blank)

- 17 (blank) Diseases of epididymis and spermatic cords
- 170 Diseases of testis (including orchitis)

171 Diseases of scrotum (such as hydrocele, varicocele, spermatocele)
172 Diseases of penis (such as redundant prepuce, chancroid)
173 Disease of prostate and seminal vesicles (such as prostatic hypertrophy, prostatitis, periprostatic abscess)
174 General (including impotence, premature ejaculation, neuroses)
175-178 Blank
179 Miscellaneous

18 blank to 189 Diseases of female reproductive system (except 03, 3 blank to 59 and 27 blank)

18 (blank) Diseases of vagina and genitalia
180 Diseases of uterus
181 Diseases of tubes
182 Diseases of ovaries
183 Abnormalities of pelvic floor
184 Pelvic peritoneum (including inflammation, adhesions, abscess and others)
185 Abnormalities in menstruation
186 General (including neuroses)
187-188 Blank
189 Miscellaneous

19 blank to 199 Special abnormalities or diseases associated with pregnancy (except 14, 3 blank to 59 and 26 blank to 269)

19 (blank) Abnormal pelvis
190 Normal pregnancy
191 Toxemias of pregnancy (including pernicious vomiting, eclampsia annd others)
192 Abortions and premature labor
193 Complications of labor
194 Complications of puerperium
195-198 Blank
199 Miscellaneous

20 blank to 209 Diseases of skin, hair and nails (except 0 blank, 01 to 03, 06 to 10, 14, 15, 17 to 19, 3 blank to 59, 82 to 86, 21 blank to 219, 264, 27 blank and 28 blank to 289)

20 (blank) Cocogenous infections (including impetigo, ecthyma, furuncles, carbuncles, abscess, folliculitis, sycosis vulgaris and acne vulgaris)
200 Toxic dermatitis (including toxic erythemas, erythema multiforme, erythema nodosum, urticarias, occupational dermatitis, drug sensitizations)
201 Mycoses, tricophyton group (including favus, versicolor, epidermamycosis)
202 Inflammatory diseases (etiology unknown or uncertain, including psoriasis, pityriasis rosea, eczemas, lichen planus, herpes zoster, herpes simplex, pemphigus, seborrhea)
203 Hypertrophies and atrophies (including clavus, callositis, verruca, ichthyosis, vitiligo, keloid)
204 Dermatitis venenatas and dermatitis of external causes (including plants in general, paints, phosphorus and roentgen ray or radium)
205-208 Blank
209 Miscellaneous

21 blank to 219 Diseases of ductless glands exclusive of spleen (except 3 blank to 69 and 17 blank to 189)

21 (blank) Hyperthyroidism (including goiter, toxic adenomas, thyroiditis)
210 Myxedema, cretinism and low basal metabolic rates
211 Simple and colloid goiters
212 Diseases of pituitary
213 Other endocrine disturbances
214-218 Blank
219 Miscellaneous

22 blank to 229 Diseases of eye (except 03, 06, 3 blank to 59, 264 and 27 blank)

22 (blank) General
220 Lids and lacrimal apparatus
221 Conjunctiva
222 Cornea (such as pterygium)
223 Anterior chamber and sclera
224 Errors in refraction
225 Lens retina and optic nerve (such as vision blindness, optic neuritis)
226 Uveal tract, iris, ciliary body, choroid and vitreous
227 Eyeball, orbit, disturbances of motion
228 Blank
229 Miscellaneous

23 blank to 239 Diseases of ear (except 3 blank to 59, 264 and 27 blank)

23 (blank) General
230 Auricle
231 External and auditory canal
232 Eustachian tube
233 Middle ear and mastoid cells
234 Internal ear—semicircular canals
235 Internal ear—cochlea
236 Special disturbances in hearing
237-238 Blank
239 Miscellaneous

24 blank to 259 Diseases of nervous system (except 0 blank to 59 and 26 blank to 269)

24 (blank) Multiple sclerosis
240 Arteriosclerosis of the central nervous system
241 Congenital and familial disease
242 Progressive muscular dystrophy and myasthenia gravis
243 Hyperkinetic diseases (such as chorea, paralysis agitans, tics, epidemic encephalitis)
244 Head injuries involving brain
245 Spinal injuries involving cord
246 Neuralgias and neuritis
247 Migraine
248 Epilepsy and epileptiform convulsions
249 Other general diseases of central nervous system

25 (blank) Other diseases of meninges
250 Other diseases of brain
251 Other diseases of cranial nerves
252 Other diseases of peripheral nerves

253 Other diseases of spinal cord
254-258 Blank
259 Miscellaneous

26 blank to 269 Abnormal mental conditions
26 (blank) Organic conditions (except 3 blank to 39 and 24 blank to 259)
260 Dementia praecox group
261 Manic depressive group
262 Mental deficiency
263 Constitutionally psychopathic personalities
264 Minor psychoses (including hysterias, traumatic and occupational neuroses, except 94, 112, 174, 186)
265 Environmental maladaptations (including all types of mental conflicts)
266 Symptomatic conditions (including deliriums and coma)
267-268 Blank
269 Miscellaneous

27 blank to 279 Constitutional and developmental abnormalities
27 (blank) Congenital abnormalities (except 32, 35, 241)
270 Defective physical development
271 Fetal monstrosities
272-278 Blank
279 Miscellaneous

28 blank to 289 Environmental causes of injury and disease
28 (blank) Physical environmental conditions (including heat, sun, exposure, light, dust and humidity)
280 Poisonings (including food, drugs, serum sickness)
281 Alcoholism and drug addiction
282 Wounds, abrasions, contusions, bruises, sprains
283 Dislocations
284 Fractures
285 Burns
286-288 Blank
289 Miscellaneous

29 blank to 299 Bones, muscles, fascia and locomotor system in general (except 03, 14, 3 blank to 59, 28 blank to 289 and 31 blank to 319)
29 (blank) Bone deformities (including osteomyelitis, periostitis and others)
290 Bone diseases (including osteomyelitis, periostitis and others)
291 Other bone abnormalities and diseases
292 Diseases of joints (including arthritis and ankylosis)
293 Diseases of muscles (except 242)
294 Diseases of fascia and tendons (including cellulitis)
295 Diseases of bursae
296-298 Blank
299 Miscellaneous

30 blank to 309 Miscellaneous medical conditions or diseases

UNASSIGNED

31 blank to 319 Miscellaneous surgical conditions or diseases
31 (blank) Inguinal and femoral hernias
310 Other types of hernias
311 Gangrenes, all types

312-318	Blank
319	Miscellaneous
32 blank to 329	*Special pediatric and child-welfare conditions*
32 (blank)	Stillborns
320-328	Blank
329	Miscellaneous
33 blank to 389	*(Six unassigned major subdivisions)*
39 blank to 399	*Miscellaneous*
39 blank to 398	Blank
399	Miscellaneous

In case most of the records of an institution belong to some special service, it would be desirable to code this particular section of the diagnostic code to the third column. For example, let us consider a set of records made up of dermatologic patients. The special section for skin is from 20 blank to 209. Each of these eleven headings can be subdivided by the third column into eleven subheadings, making one hundred and twenty-one possibilities in this section. But dermatologic observations would also be listed in other sections of the diagnostic code: one or two under 0 blank; about five under 01; from five to eight under 09; eleven under 33; eleven under 44; eleven under 52; from five to ten under 21 blank to 219; from ten to twenty under 27 blank to 279; eleven under 282; eleven under 285 and eleven under 311, a total of at least 200 subdivisions.

There are six major headings, 33 blank to 389, which are unassigned, each containing 121 possible entries. Any or all of these could be used for dermatology if desired. By this means the diagnostic code has been kept elastic, permitting the assignment of code divisions according to the major interests in the hospital.

Code for Age.—The code for age occupies columns 22 and 23. Birth is represented by 00 and the years from 1 to 98 by the identical number on the card. Number 99 indicates 99 years and over. Column 23 is used a second time for age in the first year by the blank position being punched instead of the zero in column 22. This distinguishes the unit numbers from 0 to 9 in column 23 as to whether they are preceded by a zero or a blank. The first year of age is coded as follows: blank 0, under 1 week of age, except new-born; blank 1 from 1 to 2 weeks; blank 2, 2 to 3 weeks; blank 3, 3 weeks to 1 month; blank 4, 1 to 2 months; blank 5, 2 to 3 months; blank 6, 3 to 4 months; blank 7, 4 to 6 months; blank 8, 6 to 9 months; and blank 9, from 9 to 12 months.

Code for Sex and Color.—The code for this is indicated in column 24. Male white is indicated by 0; male black by 1; female white by 2; female black by 3; and information on sex or color unknown or not recorded by 4.

Code for Civil State and Outcome.—In order to save space, it was necessary to code civil state and outcome together in column 25 by a combination code. Both civil state and outcome are divided into three parts. Code no. 0 signifies outcome well, civil state single; no. 1, outcome well, civil state married; no. 2, outcome well, civil state divorced, widowed or separated; no. 3, outcome dead, civil state single; no. 4, outcome dead, civil state married; no. 5, outcome dead, civil state divorced, widowed or separated; no. 6, outcome improved, same or worse, civil state single; no. 7, outcome improved, same or worse, civil state married; no. 8, outcome improved, same or worse, civil state, divorced, widowed or separated. The code number for column 25, therefore, represents one of the nine possible combinations between the two items of outcome and civil state. In the illustrative diabetic case, civil state is recorded as married, outcome improved, and it therefore is indicated by a code number 7 in column 25.

Code for History, Columns 26 to 29.—The code for the history is as follows:

(a) Past illness column 26 (including weight curve fig. 1 p. 6): 1, typhoid to scarlet fever; 2, syphilis and gonorrhea and abnormal weight curve; 3, accidents and operations; 4, operations on the nose and throat; 5, miscellaneous past illnesses not included in 1 to 4.

(*b*) Respiratory, circulatory and gastro-intestinal systems, column 27: 1, respiratory system; 2, circulatory system; 3, gastro-intestinal system,—appetite to jaundice; 4, gastro-intestinal system, remaining items; 5, miscellaneous items for respiratory, circulatory and gastro-intestinal systems, not listed under 1 to 4.

(*c*) Genito-urinary and nervous systems, column 28: 1, Genito-urinary system; 2, nervous system, sense of exhaustion to mental conflicts; 3, nervous system, ear; 4, nervous system, eye; 5, miscellaneous under genito-urinary and nervous systems not included in 1 to 4.

(*d*) Family history, marital history, menstrual history, habits and inaccuracy of history, column 29; 1, family history; 2, marital history; 3, menstrual history; 4, habits, and 5, inaccuracy of history.

Code for Body Weight.—Body height is coded in inches in column 30; blank, unknown; 0, under 24; 1, from 24 to 29; 2, 30 to 35; 3, 36 to 41; 4, 42 to 47; 5, 48 to 53; 6, 54 to 59; 7, 60 to 65; 8, 66 to 71; and 9, 72 and over. Mrs. H. Brown had a height of 64 inches indicated by a code number of 7 in column 30.

Code for Body Weight.—The code for body weight is indicated in column 31 in pounds, blank, unknown; 0, under 20; 1, from 20 to 39; 2, 40 to 59; 3, 60 to 79; 4, 80 to 99; 5, 100 to 129; 6, 130 to 159; 7, 160 to 189; 8, 190 to 219; and 9, 220 and over. Mrs. H. Brown had a body weight of 160 pounds which is indicated by a code number of 7 in column 31.

Code for Physical Examination, Columns from 32 to 39.—The code for the physical examination follows:

(*a*) Abnormalities in temperature and abnormalities of the head and face are coded in column 32: 1, temperature; 2, head and face, hair to eyes; 3, head and face, ears; 4, head and face, nose and jaw, and 5, miscellaneous under head and face not listed under 2, 3 and 4.

(*b*) Abnormalities of the mouth and throat, column 33: 1, lips, gums and teeth; 2, tongue, palate and pharynx; 3, tonsils; 4, larynx, and 5, miscellaneous under mouth and throat, not included in 1 to 4.

(*c*) Abnormalities of the neck, spine and thorax, column 34: 1, neck; 2, spine; 3, general respiratory tract and breast; 4, inspection of thorax, and 5, miscellaneous items under neck, spine and thorax, not included in 1 to 4.

(*d*) Abnormalities of the chest and lungs, column 35: 1, inspection; 2, tactile fremitus and percussion; 3, abnormal breath sounds, whispered voice and spoken voice; 4, râles and friction rub, and 5, miscellaneous under chest and lungs not recorded in 1 to 4.

(*e*) Abnormalities of the heart and rate of heart, column 36: 1, inspection and palpation; 2, percussion and abnormal outline of heart; 3, auscultation; 4, rate of heart at apex and pulse, and 5, miscellaneous abnormalities of heart not listed under 1 to 4.

(*f*) Abnormalities of the vessels and abdomen, column 37: 1, vessels; 2, inspection of abdomen; 3, palpation of tenderness, rigidity and abdominal organs; 4, palpation of mass and inguinal rings, and 5, miscellaneous under abdomen not included in 1 to 4.

(*g*) Abnormalities of the extremities and neurologic symptoms, column 38: 1, club digits to varicose ulcer; 2, motor; 3, joints; 4, neurological, and 5, miscellaneous under extremities and neurological not included in 1 to 4.

(*h*) Abnormalities of the lymph nodes, skin, genitalia, rectum and psyche, column 39: 1, lymph nodes; 2, skin; 3, genitalia; 4, rectum, and 5, psyche. The miscellaneous of the various groups in this section are included with the respective subdivisions.

Code for Laboratory Observations, Columns 40 to 43.—The code of laboratory observations follows:

(*a*) Abnormalities in the examination of urine, blood, Wassermann reaction, spinal fluid, sputum, throat culture, blood culture and Widal, column 40: 1, indicates urine; 2, blood from hemoglobin to white blood cell count; 3, blood from platelets to comment; 4, Wassermann and spinal fluid, and 5, sputum, throat culture, blood culture and Widal.

(*b*) Abnormalities of the following, column 41: 1, signifies blood chemistry; 2, basal metabolic rate and electrocardiograph report; 3, cystoscopic and phthalein examination; 4, proctoscopic, stool and fractional test meal, and 5, examination of the ear, nose and throat.

(*c*) Abnormalities of roentgen-ray and dental examination, column 42: 1, roentgen-ray examination of the head, neck and thorax; 2, of skeleton spine, extremities and pelvis; 3, of gastro-intestinal tract; 4, of abdominal viscera, urinary system and miscellaneous, and 5, dental examination, including roentgen-ray of teeth.

(*d*) Abnormalities in examination of the eye and miscellaneous laboratory tests, column 43: 1, examination of the eye; 2 and 3, laboratory tests, beginning with letters a to l; 2, normal; 3, abnormal; and 4 and 5, laboratory tests, m to z; 4, normal; 5, abnormal.

There are probably from 100 to 200 miscellaneous laboratory tests. It is considered desirable to split this total number into two parts, and this is accomplished alphabetically. The first letter in the technical name of the test is used for the purpose. For example, if a patient should have a sugar tolerance test that was abnormal it would be coded as item 5, column 43. If the test was normal, it would be represented by code no. 4.

Code for Miscellaneous, Columns 44 and 45.—Columns 44 and 45 permit space for listing ten abnormalities in which the institution or the physician is especially interested. We suggest the following uses for these two columns:

In column 44, 1, signifies autopsy; 2, a major operation; 3, a minor operation on the nose or throat or a dental extraction, and 4, previous admissions. Columns 45 may be retained as a service column to indicate the principal service on which a patient is examined and treated. At least five services would be required by almost all hospitals, namely—medicine, surgery, gynecology, obstetrics and pediatrics. Other subdivisions about twenty in all could be noted. The coding would be as follows: 00, medicine; 01, medicine and some other service; 02, surgery; 03, surgery and some other service; 04, gynecology; 05, gynecology and some other service, and so on. The even numbers could be listed up to twenty different services, and the odd numbers could be retained for patients in these respective services who were also treated in some other hospital service.

DESCRIPTION OF THE TECHNIC OF PUNCHING CARDS AND WHAT IT MEANS TO THE RECORD DEPARTMENT OF THE AVERAGE HOSPITAL

The machine used to punch the index card is simple in construction and easy to use (fig. 7). This machine and a few filing boxes represent the only special equipment necessary for the installment of the index in the average hospital. Punch machines can be rented by the month from both the Powers and International Tabulating Machine Companies, or the hand instrument of the type in the diagram can be purchased from the International Time Recording Company. The nonelectrical type of punch machine would be adequate for the needs of all smaller hospitals.

The punch card is placed on a moving platform as observed in figure 7. The keys are struck one at a time for any desired number. As the

key is punched, the machine automatically moves the card to the next column. Its action in this respect is similar to that of a typewriter.

The safest way to check the punch card is to have the clerk punch a set of cards and then punch a second set from the same original observations. If the corresponding cards in the two sets are superimposed and held to the light, a glance is sufficient to see that all the holes are punched similarly. This process reduces the error due to the personal equation to an extremely low probability.

A filing clerk can be trained to carry on this system in about two weeks' time. An expert can punch about 2,000 cards during an eight hour day. A clerk of average ability will have no difficulty in coding, punching and checking at least 100 cards a day. This is an average daily discharge rate greater in magnitude than any except that of the largest hospitals in the country.

It will be necessary for the hospital to provide from three to four filing boxes to keep these punch cards for a period of from six months to a year. One box will hold from 1,500 to 2,000 cards.

DESCRIPTION OF THE PRINTED CROSS-INDEX

After the punch cards have accumulated for three, six or twelve months, they are sent away and made up into a printed cross-index. The index cards described for this system were designed for the Powers Printing Tabulator. Cards might be equally well designed for the International Tabulating Machine. The printed record which is returned to the hospital will list the information on these index cards in every desired fashion, so that it is unnecessary to keep the cards after the printed record has been returned.

The description of this printing process does not concern the hospital. The printed record which is returned to the hospital is in the form of a loose-leaf, postbound index. A page will be set aside in this index for each of the various diagnoses and the major divisions in the history, physical examination and laboratory observations. For example, figure 8 shows a sample page, entitled diabetes mellitus; the fifth printed line of figures on this page represents the complete index record of the illustrative diabetic case of Mrs. H. Brown. Every coded item on her index card (fig. 6) is printed on this one line of type. This same line of type signifying all the important facts about the case will be printed on thirty other pages in the cross-index. It will appear on all of the pages entitled with the abnormalities which are indicated as positive for her case; for instance, it will be listed on the pages entitled obesity, acidosis, arteriosclerosis, hypertension, constipation, hemorrhoids, positive items 1, 2, 3 and 4 from past illness; positive respiratory history; positive circulatory history; abnormal gastro-intestinal history, item 4;

abnormal nervous system history, item 2; abnormal family history; abnormal observations on the eye and mouth and throat no. 2; abnormal observations on the neck; râles and friction rub; abnormal observations on the heart, item 3; abnormal vessels; abnormal observations on the skin; abnormalities of the rectum; abnormalities in psyche; abnormal urine; abnormal blood chemistry; abnormal observations on the ear, nose and throat; abnormal roentgenogram of the head, neck and thorax; abnormal results from dental examination; and abnormal observations following examination of the eye.

The physician can turn to any one of these index pages and find the complete entry of all coded facts for the case of Mrs. H. Brown.

For the sake of illustration we have coded the information in several other diabetic cases. The abnormal observations in each case are listed as a single line of type in figure 8. Therefore, if the physician desires

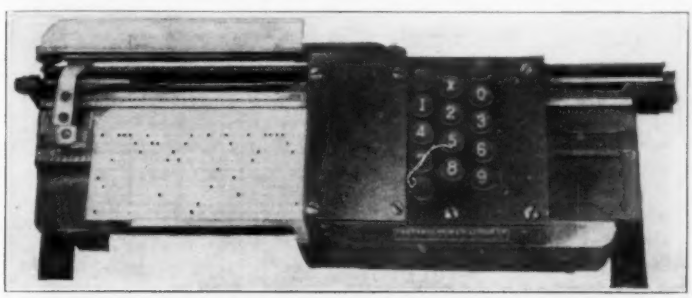

Fig. 7.—Machine used for the punching of index cards.

to obtain the diabetic cases of those patients who also had arteriosclerosis and cardiac symptoms, and who were more than 50 years of age, he would turn to this index page entitled diabetus mellitus in the printed volume and locate the record of those patients who had arteriosclerosis (code no. 80); this would involve cases 53123, 59106 and 67190. Of these three patients, a glance at columns 22 and 23 demonstrates that only the first two patients were more than 50 years of age and of these two only one, 59106, in column 36, showed positive cardiac symptoms.

It is planned that these printed cross-index sheets will be bound in loose-leaf volumes and that the volumes will increase in size from year to year as a continuous loose-leaf, postbound index. For example, tabulation of diabetes mellitus for 1927 will immediately follow the diabetic cases for 1926, and in this way all the diabetic cases over the entire period of the hospital record system will be noted in the same position of the cross-index. This is a material advantage, since only one search will be necessary for any given type of abnormal observations.

From six to eight duplicates of the printed index file can be made if desired. This makes it possible for several departments of the hospital, or for hospitals in different parts of the country to have at hand a complete index of all cases in any given institution. Loss or destruction of an index is practically impossible if duplicates are made.

ESTIMATION OF COST OF MECHANICAL INDEX SYSTEM

The cost of this index will vary somewhat with the number of case records involved. Several items enter into the estimate, namely, the purchase or rental of a machine to punch the index cards, the purchase of index cards—which should not amount to more than a few dollars a year for the average hospital—the wages of a clerk for from one-half to full time depending on the size of the hospital and the efficiency

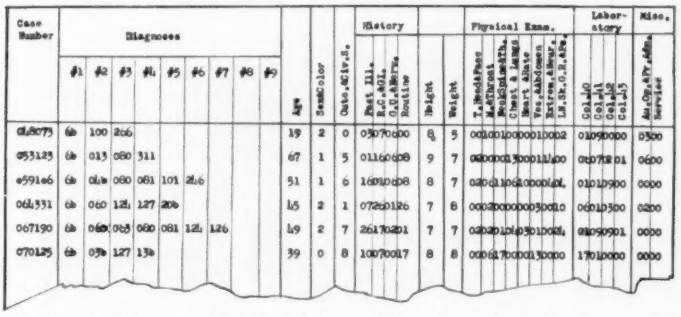

Fig. 8.—Sample page labeled diabetes mellitus from the printed cross index. The information given on index card, figure 6, appears as the fifth printed line of type.

of the clerk, the purchase of from two to eight boxes as a temporary file for punch cards and the cost of the printed cross-index.

The printing of the cross-index represents the only formidable item in this list. If a number of hospitals accepted the same index set-up, the price for each would be considerably reduced. It would be possible to reduce this expense to a great degree if some medical institution would rent a set of tabulating machinery and make up the printed cross-indexes for a dozen or more hospitals. The total expense for the printing could then be divided and would become a minor consideration in the sums allotted the record department.

It is probable that the installation of this mechanical index-system would release some clerical expense and save considerable time involved at present in the search for records. We believe, although we have not been able to test the matter by actual trial, that the expense

involved in the system would be equal approximately to that of maintaining the present average cross-index and that it would not be an excessive burden even if it were superimposed on an existing system.

SUMMARY OF ARGUMENTS IN FAVOR OF THE MECHANICAL CROSS INDEX

The mechanical cross-index, as here outlined, fulfils the features that seem to be desirable for a hospital index.

1. It would be possible to locate the case number of records desired by the physician within a few minutes' time regardless of inaccurate information in respect to the patient's name.

2. It would do away with misplacement of records due to multiple or ambiguous diagnoses.

3. It permits the location of records by history and physical examination as well as by diagnoses.

4. It fills the need of a small hospital with about the same efficiency that it does a larger institution.

5. It is elastic, and can be adapted to any type of special interest in medical work.

6. After the coding is understood and the routine established, one clerk can handle the entire index system regardless of the size of the hospital.

7. The expense approximates the present outlay for the average cross-index in use by most hospitals. It must be realized in this connection that the cost of such an index would be prohibitive unless a systematic case record form of the general type proposed in this article is used. In the ordinary case history now in vogue in hospital practice, the coding feature would be a major consideration, and an almost insurmountable barrier.

CHRONIC SPLENOMEGALY*

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During the last twenty-five years, surgeons have attempted to add surgical treatment to other forms of therapy in many conditions characterized by anemia and splenomegaly. They have, therefore, applied splenectomy in advanced, and in some early, cases of splenic anemia, hepatic cirrhosis, hemolytic icterus, pernicious anemia, myelogenous leukemia, Gaucher's[1] disease, and recently, to hemorrhagic purpura. Their efforts have been beneficial in splenic anemia, hemolytic icterus and hemorrhagic purpura, but rather unsatisfactory in pernicious anemia and in myelogenous leukemia. Occasionally splenectomy in hepatic cirrhosis is followed by improvement. Removal of the spleen as a therapeutic procedure has been based on the facts that it may be removed without definite damage to life; that this organ may be a factor in the destruction of blood in some cases of anemia; that any tumor which interferes with the vital functions of other organs should be removed, and that splenectomy empirically performed in hemorrhagic purpura is unquestionably followed by an almost immediate and permanent rise in the blood platelet count with prevention of further purpura. In general, these facts account for the relatively large number of spleens which have been studied in making this series of observations. Heretofore most of the information relative to this organ's normal and abnormal structure and function has been obtained from material observed at autopsy and from experimental animals. It has seemed wise, therefore, to examine those spleens which have been removed at operation.

In reviewing the literature on hematology and the normal structure and function of the spleen, one is impressed principally by the confusion in nomenclature and by the great differences in observations and opinions. An attempt, therefore, has been made to make original observations without being biased by previous reading. The nomenclature for cells is that which I described in 1919.[2] At that time all names of adult cells ended in cyte, and all regenerative types of cells in blast; thus the red blood corpuscle was called an erythrocyte and a nucleated red cell (normoblast, etc.) an erythroblast. Instead of using the term myelocyte, the immediate progenitors of the leukocytes were called leukoblasts. A regenerative stage or form of an endotheliocyte was called an endo-

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* A preliminary report.

1. Gaucher: Bull et mém. Soc. méd. d. hôp. de Paris **60**:630, 1892.

2. MacCarty, W. C.: A Biological Conception of Neoplasia, Its Terminology and Clinical Significance, Am. J. M. Sc. **157**:657, 1919.

thelioblast. This uniformity of terminology has served a useful purpose in the study of the relationship of cells to other cells and of their morphology in relation to biologic behavior. Besides the confusion in nomenclature, there has been some difference of opinion in the description of clinical entities which are associated with splenomegaly. In the following study, however, the conditions named were typical, and there was never any doubt about the clinical pictures as they have been uniformly accepted.

The material investigated was obtained from eighty-two cases of splenic anemia, fifteen of hepatic cirrhosis, fifty of hemolytic icterus, fifty-one of pernicious anemia, thirty of myelogenous leukemia, six of Gaucher's disease, and twenty of hemorrhagic purpura, making a total of 254, to which must be added a miscellaneous group of sixty-six in which the clinical picture was not definite enough to be classified but which was associated with splenomegaly. Thus 320 spleens [3] were studied with the following ideas in mind:

1. The establishment of a standard cytology regardless of the confusion in nomenclature.

2. To determine whether the histologic and cytologic splenic pictures bear any specific relation to the recognized clinical entities as they are accepted by modern diagnosticians and teachers of medicine.

3. To determine, if possible, if there might be any relation between the so-called clinical entities.

4. To obtain any possible information on the normal and abnormal structure and function of the spleen.

The normal spleen is a vascular organ in which lymph follicles are extremely numerous; the main problem for all investigators has been the establishment of correct structural relationships between the lymphatic tissues, the supporting network of connective tissue (frequently called the reticulo-endothelial tissue) and the circulating blood. Many differences of opinion may be found in the literature, and few, if any, have a perfectly clear idea of the exact structural and functional characteristics of this organ. In general, it may be said that the structural and functional unit is a complex one with the germ center at one end and the circulating blood at the other as shown in the illustration. Between the two there is a network composed of fibrocytes and their elongated fibrils which form the meshes in which lymphocytes and normal blood cells intermingle in performing the one or more functions of the organ.

3. Between 1904 and 1927, 456 splenectomies were performed in the Mayo Clinic. The material presented in this study represents only a part; other spleens have been used in the study of circulation by Passalacqua and Gay, and the connective tissue of the organ by Perez Fontana. These reports will appear in the near future.

Under normal conditions there are certain definite types of cells which are constantly found in the spleen. Thus one sees lymphoblasts, lymphocytes, fibroblasts, fibrocytes, erythrocytes, endotheliocytes and at least two (neutrophilic and eosinophilic) of the recognized leukocytes; basophilic leukocytes are rare and frequently difficult to differentiate

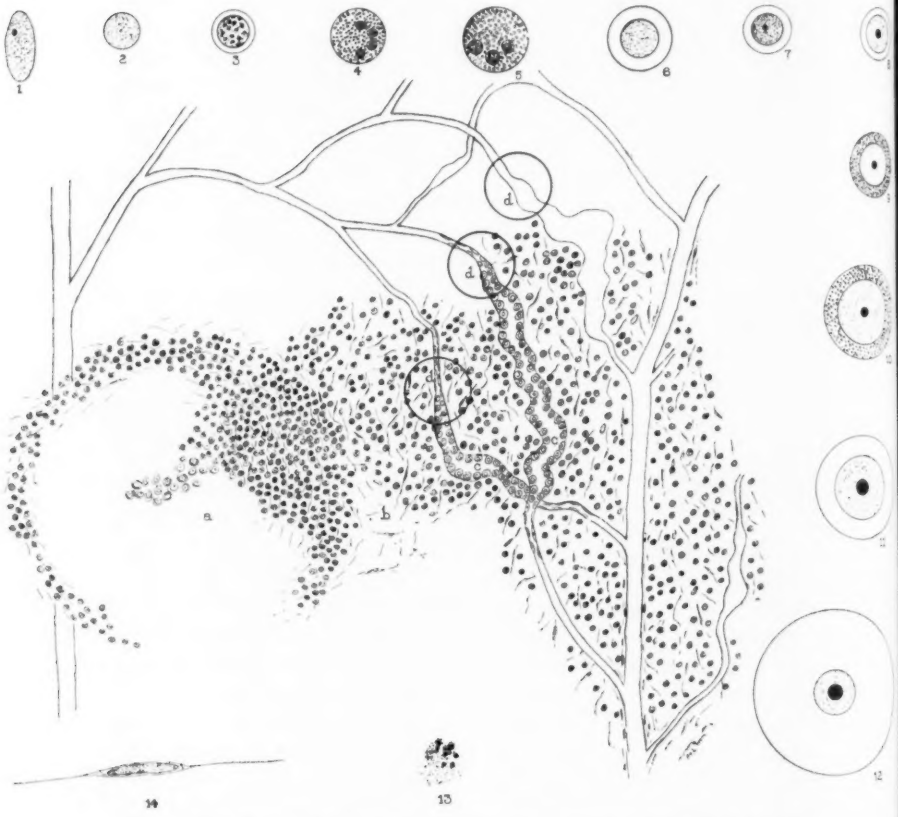

Diagram of histologic and cytologic units of the normal spleen and the cells found under pathologic conditions: *a* shows the germ center in lymph follicle; *b*, reticulum containing lymphocytes, fibrocytes and fibroblasts; *c*, the sinuses, and *d*, the disputed area in which arterial capillaries enter sinuses. (Do they become dilated into sinuses, or do they enter at stoma in the endothelial walls of sinuses?) All cells are drawn to scale from unembedded fresh material. They are as follows: 1 is a fibroblast; 2, erythrocyte; 3, lymphocyte; 4, neutrophilic leukocyte; 5, eosinophilic leukocyte; 6, endotheliocyte; 7, erythroblast; 8, lymphoblast; 9, small neutrophilic leukoblast; 10, eosinophilic leukoblast; 11, endotheliblast; 12, Gaucher cell; 13, pigment, and 14, fibrocyte.

positively from eosinophilic leukocytes; in my own studies they have been too few and uncertain to allow any conclusions relative to them and their possible relation to the subject. Under abnormal conditions such as exist in the clinical entities of this study, one sees not only quantitative proportional variations in the types of cells which are normally present, but also the presence of the younger forms—the blasts of the normal cells, as shown in the illustration. In addition one sees in varying degrees deposits of pigment which are a residue of erythrocytes which have been destroyed either in the circulating blood or in the spleen itself. The changes which one sees in splenomegaly are relative and have to do with changes in the organ dependent on the relative presence of normal cells, young cells, pigment, changes in the network of the connective tissue, obstruction to the flow of blood and reduction of normal structural units. The idea that the spleens, which are a part of each clinical entity, possess characteristic changes which differ from other clinical entities is incorrect, as will be seen in the accompanying figures. I shall consider each clinical entity separately and briefly state the things which make it an entity and then describe the conditions of the spleens.

CLINICAL ENTITIES

Splenic Anemia (Banti's Disease).—There may be some question as to whether Banti's disease is always splenic anemia or whether splenic anemia is always that picture which Banti[4] described. In the one, enlargement of the spleen is subsequently followed by cirrhosis of the liver; in the other, the spleen is enlarged without demonstrable cirrhosis of the liver. In both conditions, there is anemia without apparent changes in the morphology of the erythrocytes. Whether or not Banti's disease and splenic anemia are the same disease, both are accompanied by splenic enlargement and anemia with the other clinical conditions which accompany anemia. The spleens are grossly and microscopically indistinguishable, one from the other. For practical purposes, the two diseases are usually considered as one. In this series, the facts shown in table 1 were noted.

The most obvious things in the spleens in cases of advanced splenic anemia are the great size of the organ, replacement of pulp by dense connective tissue, relative reduction of the number of germ centers, dilatation of the sinuses and the presence of pigment which is, however, much less in amount than that found in pernicious anemia and hemolytic icterus. The cells lining the sinuses are usually small compared with those of the normal sinuses. The spleens in splenic anemia are the largest spleens in this series of conditions.

4. Banti: Ziegler's Beiträge, vol. 24.

Hemolytic Icterus.—This is perhaps a less definite and less easily recognized clinical entity than splenic anemia. It usually occurs in younger persons and even in infants. The typical picture is characterized by enlargement of the spleen, some enlargement of the liver, moderate

TABLE 1.—*Data for Patients with Splenic Anemia* *

Average age of patient	33 years
Percentage males	58
Percentage palpable spleens	94
Average weight of spleen	1,040 Gm.
Percentage showing congestion in spleen	0
Percentage showing pigment in spleen	62
Percentage showing leukocytes (neutrophilic) in spleen	67
Percentage showing leukocytes (eosinophilic) in spleen	41.5
Percentage showing germ centers in spleen	28.1
Percentage showing lymph follicles in spleen	85
Percentage showing thickened blood vessels in spleen	65
Percentage showing hyalinized blood vessels in spleen	25
Percentage showing fibrocytes	78
Percentage showing fibroblasts	90
Percentage showing atrophic endotheliocytes	68
Percentage showing normal endotheliocytes	56
Percentage showing endothelioblasts	25
Percentage showing leukoblasts (myelocytes)	13.5

* Technic.—Blocks were taken from different parts of each spleen and studied in the fresh unfixed, and fixed condition without any form of embedding. Notes on all slides were made according to a definite cytologic morphologic standard without any regard to the clinical diagnosis. They were later studied together. The percentages are only relative when comparing one disease with another; they do not represent the exact frequency of the various factors in the different disease entities, because complete serial sections were not made through all spleens.

TABLE 2.—*Data for Patients with Hemolytic Icterus*

Average age of patient	27.5 yrs.
Percentage of males	49
Percentage palpable spleens	88
Average weight of spleen	860 Gm.
Percentage showing congestion in spleen	60
Percentage showing pigment in spleen	96
Percentage showing leukocytes (neutrophilic) in spleen	32
Percentage showing leukocytes (eosinophilic) in spleen	44
Percentage showing germ centers in spleen	17
Percentage showing lymph follicles in spleen	80
Percentage showing thickened blood vessels in spleen	32
Percentage showing hyalinized blood vessels in spleen	8
Percentage showing fibrocytes	17
Percentage showing fibroblasts	52
Percentage showing atrophic endotheliocytes	41
Percentage showing normal endotheliocytes	65
Percentage showing endothelioblasts	34
Percentage showing leukoblasts (myelocytes)	11

anemia, increased erythrocytic fragility and an icteric tint to the skin. The condition is frequently differentiated with difficulty from biliary obstruction and pernicious anemia. In this series of fifty cases, the observations contained in table 2 were noted.

Pernicious Anemia.—This condition presents an anemia with a low erythrocytic count and a low percentage of hemoglobin plus variation in size, and irregularity in the shape of the erythrocytes associated with the presence of erythroblasts. Other manifestations and sequelae of anemia are frequently present. The disease is not characterized by excessive splenic enlargement, although the spleen was palpable in 45 per cent of this series of fifty-one cases. The condition has been considered a disease of the blood, but since there is an extensive destruction of erythrocytes as well as incompleteness in their production, surgeons have considered the spleen a possible source of erythrocytic destruction. This accounts for the experimental period in which splenectomy was tried as a possible good therapeutic procedure. The results have been discouraging, and one now rarely has the opportunity to see spleens of

TABLE 3.—*Data for Patients with Pernicious Anemia*

Average age of patient	47 years
Percentage of males	73
Percentage of palpable spleens	45
Average weight of spleen	350 Gm.
Percentage showing congestion in spleen	37
Percentage showing pigment in spleen	96
Percentage showing leukocytes (neutrophilic) in spleen	55.5
Percentage showing leukocytes (eosinophilic) in spleen	69.5
Percentage showing germ centers in spleen	11
Percentage showing lymph follicles in spleen	97
Percentage showing thickened blood vessels in spleen	48
Percentage showing hyalinized blood vessels in spleen	44
Percentage showing fibrocytes	16
Percentage showing fibroblasts	43.5
Percentage showing atrophic endotheliocytes	26
Percentage showing normal endotheliocytes	63
Percentage showing endothelioblasts	45
Percentage showing leukoblasts (myelocytes)	49

patients with pernicious anemia until after the inevitable death. The data for these patients are given in table 3.

The spleens of patients with pernicious anemia are not any more characteristic than those of patients with hemolytic icterus, and both have some things in common. In both there is a large amount of pigment; this is much greater than is found in any other splenic condition in this series. In pernicious anemia the disease is apparently one which manifests itself in the spleen by erythrocytic destruction, pigmentation, and the increased presence of leukocytes and leukoblasts. There is an apparent increase in the presence of endothelial regeneration in the sinuses manifested by endothelioblasts. Chronicity is not so evident, as may be seen in the apparent absence of connective tissue proliferation, although there is evidence of its early stages as seen in the increase in the number of fibroblasts. The blood vessels show an unusual amount of hyalinization and thickening.

Myelogenous Leukemia.—The condition in myelogenous leukemia is characterized by anemia plus the presence of myelocytes (leukoblasts) in the circulating blood and tissues. It is usually associated with splenic enlargement. For a short period, the patients with the condition were treated empirically by splenectomy, with poor results. In this series, there were thirty spleens which showed the features given in table 4.

TABLE 4.—*Data for Patients with Myelogenous Leukemia*

Average age of patient	37 years
Percentage of males	31
Percentage of palpable spleens	100
Average weight of spleen	830 Gm.
Percentage showing congestion in spleen	3
Percentage showing pigment in spleen	74
Percentage showing leukocytes (neutrophilic) in spleen	57.5
Percentage showing leukocytes (eosinophilic) in spleen	38
Percentage showing germ centers in spleen	7
Percentage showing lymph follicles in spleen	80
Percentage showing thickened blood vessels in spleen	38
Percentage showing hyalinized blood vessels in spleen	3
Percentage showing fibrocytes	42.5
Percentage showing fibroblasts	48
Percentage showing atrophic endotheliocytes	32
Percentage showing normal endotheliocytes	44.5
Percentage showing endothelioblasts	64
Percentage showing leukoblasts (myelocytes)	71.5

TABLE 5.—*Data for Patients with Cirrhosis and Splenomegaly*

Average age of patient	41 years
Percentage of males	65
Percentage of palpable spleens	100
Average weight of spleen	580 Gm.
Percentage showing congestion in spleen	0
Percentage showing pigment in spleen	58
Percentage showing leukocytes (neutrophilic) in spleen	72
Percentage showing leukocytes (eosinophilic) in spleen	54
Percentage showing germ centers in spleen	16
Percentage showing lymh follicles in spleen	100
Percentage showing thickened blood vessels in spleen	25
Percentage showing hyalinized blood vessels in spleen	0
Percentage showing fibrocytes	33.5
Percentage showing fibroblasts	100
Percentage showing atrophic endotheliocytes	83
Percentage showing normal endotheliocytes	33.5
Percentage showing endothelioblasts	33
Percentage showing leukoblasts (myelocytes)	18

Cirrhosis and Splenomegaly.—In this condition, the enlargement of the spleen and anemia were not the chief and most obvious complaints. The patients were suffering from ascites, which was apparently secondary to hepatic cirrhosis. Whether these cases belong in the group of splenic anemias or not may be a question. This series includes fifteen such cases, and the data in table 5 may be of significance.

Splenomegaly.—In this group are included those cases which were characterized by excessive splenic enlargement without severe anemia or with no anemia and no ascites. They may belong in the group or splenic anemia without the characteristic anemia or in the group of cirrhosis without ascites. If they belong to either group, they represent a stage of the disease in which the general or extrasplenic manifestations are absent. The facts observed are shown in table 6.

Gaucher's Disease.—This condition, which has the clinical characteristics of splenic anemia, is differentiated from splenic anemia merely by the so-called endothelial proliferation in the splenic sinuses. In general, the spleens have the gross and microscopic appearance of those in cases of splenic anemia. If, however, the endothelial proliferation is exten-

TABLE 6.—*Data for Patients with Splenomegaly*

Average age of patient	43.5 yrs.
Percentage of males	56
Percentage of palpable spleens	100
Average weight of spleen	920 Gm.
Percentage showing congestion in spleen	9
Percentage showing pigment in spleen	60
Percentage showing leukocytes (neutrophilic) in spleen	54.5
Percentage showing leukocytes (eosinophilic) in spleen	39
Percentage showing germ centers in spleen	0
Percentage showing lymph follicles in spleen	82.5
Percentage showing thickened blood vessels in spleen	44.5
Percentage showing hyalinized blood vessels in spleen	13
Percentage showing fibrocytes	66.5
Percentage showing fibroblasts	71.5
Percentage showing atrophic endotheliocytes	68
Percentage showing normal endotheliocytes	41
Percentage showing endotelioblasts	18
Percentage showing leukoblasts (myelocytes)	13

sive, the cut surface of the organ presents a mottled appearance; there are darker areas which are composed of masses of the so-called Gaucher cells. The condition as seen in a few cases has been well described by Wilson [5] and Griffin [6] and Mayo.[7] During the last year, Perez Fontana in his studies of connective tissue in the spleen has also included results of studies made at the Mayo Clinic on Gaucher spleens and has come to the conclusion that the typical Gaucher cell is not an endothelial cell, but that it belongs to the fibroblastic group and is therefore a part of

5. Wilson, L. B.: The Pathology of Splenomegaly: A Study of the Operative and Autopsy Material from the Mayo Clinic, Surg. Gynec. Obst., 1913.

6. Giffin, H. Z.: The Diagnosis of Diseases Associated with Enlargement of the Spleen, Journal-Lancet, 1913, p. 97.

7. Mayo, W. J.: Surgery of the Spleen, Surg. Gynec. Obst., 1913; The Relation of the Spleen to Certain Chronic Purpuras, Surg. Gynec. Obst. **40**:771 (June) 1925.

the reticulum. He maintains that the spleen has the elemental structure of the omentum and that, as in the omentum, the fibroblasts become large and are filled with lipoid material, thus forming the fat cells of that organ. From Fontana's observations which I have had occasion to study, his contention seems correct; the Gaucher cells are probably not endothelial and are usually outside of the sinuses. This is, however, probably only of academic importance and does not have any apparent bearing on a practical conception of the disease, which seems to behave like splenic anemia with a more rapidly fatal course. The specimens in this series are too few to permit any conclusions in relation to other types of splenomegaly.

Hemorrhagic Purpura.—In this group are included cases characterized by "chronic recurrent types of purpura hemorrhagica with low platelet count, nonretractile clot, long bleeding time and positive tourniquet or capillary resistance test. In many cases, petechiae and ecchymoses dated from childhood. Bleeding in most cases was from the nose, gums and uterus" (Giffin [8]). Bleeding from the bowel occurs in some cases. The spleens appear normal, although slightly increased in size; they do not show anything especially characteristic in this series, and they are too few for any definite conclusions to be drawn.

SUMMARY OF ITEMS NOTED

Age.—It may be seen that splenic anemia or Banti's disease is a disease which occurs during early life, appearing on the average of ten years earlier than does pernicious anemia, cirrhosis with splenomegaly or uncomplicated splenomegaly. It occurs, however, about ten years later in life than hemolytic icterus, and it appears at about the same period in life as does myelogenous leukemia.

Sex.—Splenic anemia, pernicious anemia, cirrhosis with splenomegaly and uncomplicated splenomegaly are much more common in males, while myelogenous leukemia is more common in females; hemolytic icterus occurs about equally in both sexes.

Size and Weight of Spleen.—The smallest spleens in this series occur on the average in patients with pernicious anemia, and therefore are less frequently palpable. In all other conditions the great size and associated weight make them palpable in practically all cases in which operation has been performed. This fact does not mean that in all conditions which belong to splenic anemia, hemolytic icterus, myelogenous leukemia, hepatic cirrhosis and uncomplicated splenomegaly, the patients have large spleens. In general, when the diagnosis is made the spleens are easily palpable, but in all probability there are stages in the diseases when the

8. Giffin, H. Z., and Holloway, J. K.: A Review of Twenty-Eight Cases of Purpura Haemorrhagica with Splenectomy, Am. J. M. Sc. **170**:186, 1925.

spleens are not so large. There was a time, not more than twenty years ago, when most if not all recognizable types of carcinoma of the stomach were palpable, but at present, as observed in modern clinics, many of the types of gastric carcinoma are not palpable. It may be possible that the condition of knowledge relative to splenic conditions is in the stage in which one sees only the large spleens that are present in the late stages of the disease.

Congestion and Pigmentation.—Congestion in the spleen is probably not unlike that in any other part of the body. It is an accompaniment of early active irritation, actual partial vascular obstruction or a low grade irritation without rapid production of scar tissue. As such it is more marked in youth, and when present later in life, it occurs in regions in which previous destruction has not occurred. It is most marked in hemolytic icterus and pernicious anemia, one condition occurring in early life and the other in middle life. Both diseases are accompanied by and characterized by erythrocytic pigment in the spleen, despite the fact that they do not show evidence of old chronic changes. Both diseases are relatively acute. The fact that one is usually cured by removal of the congested organ and the other is not cured by the same treatment suggests that in one the congestion may have its primary cause in the spleen, while in the other the congestion is secondary to an attempt to care for products of destruction originating elsewhere in the body. Pigmentation occurs in all of this series of spleens, but it exists only in small quantities in all but hemolytic icterus and pernicious anemia.

Neutrophilic Leukocytes.—When these cells are present in great numbers in any localized area of the body, or when they are increased in the circulating blood, an acute infection is usually indicated. In none of this series of conditions was there a great increase in their number. They are present, but there is too great a similarity in their relative presence to allow speculation concerning their significance. They are least frequent in hemolytic icterus.

Eosinophilic Leukocytes.—Like the neutrophilic leukocytes, they are not so common. One observation may be of significance: The pigment in all types of enlarged spleens of the series is usually found in eosinophilic leukocytes. In some of the fibrotic spleens, such as those found in patients with splenic anemia, hepatic cirrhosis and uncomplicated splenomegaly, much of the pigment is extracellular. In pernicious anemia, in which eosinophilic leukocytes are particularly common, they contain much pigment.

Lymph Follicles and Germ Centers.—These are present in all spleens of the series, and their relative number and presence show little differences. In general, the figures show that the lower the average age the

more prominent is their presence. The germ centers in the fibrotic spleens are less conspicuous. The exception to this may be found in the cases of splenic anemia in which the greatest number of germ centers appear. This may be due to the fact that this disease attacks people in early life, when there is normally greater regeneration of tissues. This phenomenon of regeneration is especially visible in splenic anemia; lymphoblasts of the centers and fibroblasts of the reticulum are numerous.

Thickened Walls of Blood Vessels.—The vessels especially observed in this series were those which traverse the malpighian corpuscles or lymph follicles eccentrically, since they are the small branches which are most intimate with the perifollicular reticulum and sinuses. The thickening of the wall is most marked in splenic anemia and pernicious anemia and least marked in hemolytic icterus and hepatic cirrhosis. It is found in varying degrees in all spleens in the series.

Hyalinization of the Walls of the Vessels.—Closely related to fibrosis is hyalinization, since fibrosis probably always precedes hyalinization. Marked parallelism is seen between the two conditions in the different spleens. In pernicious anemia, however, hyalinization is common and occurs in a much higher percentage of spleens than in all other conditions.

Increase in Fibrocytes and Fibroblasts.—In an organ which is normally not composed of great numbers of fibrocytes, their easily recognizable increase may be interpreted as a replacement of other structures which have been destroyed. The absence of fibroblasts in great numbers in the presence of great numbers of fibrocytes suggests a completed process, but when both fibrocytes and fibroblasts are present, one may perhaps rightly consider that the process of destruction and replacement is incomplete. In splenic anemia, both types of cells are abundant. This may also be said of uncomplicated splenomegaly, although both fibroblasts and fibrocytes are in general less frequent than in splenic anemia. In hepatic cirrhosis the spleen does not contain fibrocytes in great abundance, but fibroblasts are in greater abundance than in any other condition. This suggests that the process of replacement in the spleen is active, and that it is not of so long a duration as in splenic anemia. The relatively small number of fibroblasts and fibrocytes in hemolytic icterus, pernicious anemia and myelogenous leukemia suggests the comparative absence of destruction of the splenic tissues in these diseases.

Atrophic Endotheliocytes of the Sinuses.—There is an interesting parallelism between the increase in the fibroblasts and fibrocytes and the presence of these atrophic endotheliocytes. All three are conspicuously increased in splenic anemia, hepatic cirrhosis with splenomegaly and

uncomplicated splenomegaly, and are conspicuously infrequent in hemolytic icterus, pernicious anemia and myelogenous leukemia.

Normal Endotheliocytes of the Sinuses.—The sinuses in hemolytic icterus, pernicious anemia and splenic anemia show a higher percentage of apparently normal endotheliocytes. Their presence seems to be inversely proportional to the presence of increased fibrocytes, with the exception of splenic anemia in which fibroblasts and fibrocytes are greatly increased. This may be explained, perhaps, on the ground that splenic anemia is a disease of young persons and occurs rather acutely before atropic changes have a chance to occur in the sinuses.

Endothelioblasts Lining the Sinuses.—These cells are characterized by being large and containing large nuclei and nucleoli. They line the sinuses under certain conditions, being especially abundant in myelogenous leukemia. They are sometimes seen in all other conditions, but their increased presence in myelogenous leukemia suggests some possible relationship between the abnormal abundance of leukoblasts in the circulating blood and the tissues. This suspicion is greatly enhanced by virtue of the fact that many of these cells contain protoplasmic granules, although these granules are usually smaller than those seen in leukoblasts. Endothelioblasts are also common in pernicious anemia.

Leucoblasts (Myelocytes).—In the present work, distinction is not made between the neutrophilic, eosinophilic and basophilic leukoblasts. They are more common in myelogenous leukemia. They are next more frequent in pernicious anemia. There seems to be a parallelism between their presence and the abundance of endothelioblasts lining the sinuses.

In this brief report there seems to be no way of recognizing the clinical entity from the splenic condition alone except in extremes of myelogenous leukemia and in different types of splenomegaly which belong to either splenic anemia or hepatic cirrhosis. In general Gaucher's disease may be recognized by the presence of the so-called Gaucher's cells, although a few of these may be found also in splenic anemia. There is some evidence to suggest a possible relationship between some of the diseases which have been described, but further study must be made before any definite report is justifiable. The problem in the normal structure of the spleens remains unsolved for the present. This has to do with the exact method of entrance of the circulating blood into the so-called sinuses and the relation of the sinuses to the splenic veins.

ABSTRACT OF DISCUSSION

DR. WARD J. MACNEAL, New York: It is possible to recognize a definite anatomic unit of the structure of the spleen which can properly be designated as a splenic lobule, and it is easily recognized because it possesses the splenic follicle at its center. This is a new conception, I think, of the splenic unit. Second, the

arterial capillaries of the spleen terminate by opening into and becoming continuous with the intercellular spaces of the splenic pulp. This has been demonstrated in serial sections of the spleens of animals and of man and also by the experiment of injecting nucleated corpuscles of the blood of a bird into a tributary of the splenic artery so that these cells are injected into the spleen during life by arterial pressure.

Dr. William C. MacCarty, Rochester, Minn.: This winter I had the pleasure of seeing Dr. MacNeal's work. I have kept and expect to keep an open mind on the subject of the structure of the spleen and the relation of the arteries to the sinuses. I have two associates working with me now on circulation, and I am going to wait until they make their observations, compare them with Dr. MacNeal's and others and then, perhaps, draw conclusions.

THE INTRADERMAL SALT SOLUTION TEST IN TUBERCULOSIS *

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In a recent publication, Feldman and Reifsneider [1] briefly reviewed previous work with the intradermal salt solution test [2] and reported results of its use in a series of cases of nephritis. McClure and Aldrich,[3] who introduced the test in 1923, found that the elevation produced by the injection of salt solution disappeared more quickly than normally in the presence of edema or pre-edema. They [3] suggested the possibility that the rapid disappearance of the type studied in cases of edema with associated albuminuria might be due to a toxic condition of the tissues which increases their affinity for water. Results from the use of the test by Baker [4] in scarlet fever, by Lash [5] in toxemia of pregnancy, by Olmstead [6] in a certain group of cardiac cases and by Harrison [7] in pneumonia in children, tend to show a relationship between the toxicity or severity of illness of the patient and the disappearance time.

The present paper reports results obtained by the use of the intradermal salt solution test on twenty-nine patients in the tuberculosis department of the Cook County Hospital. Twenty-five of these had a

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* From the Otho S. A. Sprague Memorial Institute and the Pathological Laboratory of the Cook County Hospital.

1. Feldman, Aaron, and Reifsneider, J. S.: Arch. Int. Med., **41**:102 (Jan.) 1928.

2. The technic of the test is as follows: A small elevation is raised by the intracutaneous injection of 0.2 cc. of a sterile 0.8 per cent aqueous solution of sodium chloride. The length of time that the elevation remains palpable is noted. Normally, this time is at least one hour in children of more than 1 year of age, somewhat longer in white adults and still longer in negro adults. The tests reported here were performed mostly on the forearm, because, as has been pointed out by McClure and Aldrich, shortened time during which the elevation remains palpable due to deficient circulation is less frequently found here than in the leg.

3. McClure, W. B., and Aldrich, C. A.: Time Required for Disappearance of Intradermally Injected Salt Solutions, J. A. M. A. **81**:293 (July 28) 1923; The Intradermal Salt Solution Test, J. A. M. A. **82**:1425 (May 3) 1924.

4. Baker, W. J.: Intradermal Salt Solution Test in Scarlet Fever and Diphtheria Patients, J. A. M. A. **83**:1566 (Nov. 15) 1924.

5. Lash, A. F.: Intradermal Salt Solution Test in Normal and Toxaemic Pregnancies; Diagnostic and Prognostic Aid, Surg. Gynec. & Obst. **43**:40 (July) 1926.

6. Olmsted, H. C.: Intradermal Salt Solution Test in Cardiac Diseases in Children, Arch. Int. Med. **37**:281 (Feb.) 1926.

7. Harrison, J.: Intradermal Salt Solution Test in Lobar Pneumonia in Children, J. A. M. A. **84**:1258 (April 25) 1925.

Results of Injection of Intradermal Salt Solution Test on Twenty-Nine Tuberculous Patients

Case	Initials Race Sex Age	Diagnosis	Date of Skin Tests	Edema		Disappearance Time in Minutes in Forearm	Comment	Clinical Notes
				Arms	Legs			
1	(G. B.) Colored Male 50	Far advanced pulmonary tuberculosis, tuberculous bronchopneumonia	2/23/27 2/24/27	— —	— —	111 >400	Very sick, dyspneic; arms cold	Had been sick presumably only about 4 weeks before admission to hospital. While in the hospital, pulse rate varied from 98 to 100; temperature from 96.2 to 97.6 and was persistently subnormal. Respirations remained at 40. Patient died 2/25/27, after 4 days in hospital
2	(J. T.) Colored Male 36	Pulmonary tuberculosis	3/14/27	—	—	95	Patient dyspneic, unconscious; arm moist and cold	Had pneumonia about 2 months before admission to the tuberculosis hospital; cough, weakness and expectoration for 3 weeks; loss of weight of 20 pounds (9.01 Kg.) in 3 weeks. Urinalysis negative; tubercle bacilli in sputum. Roentgen-ray observations: encysted fluid present in field of lower left lung in peripheral portion. Patient died 3/14/27, after 6 weeks in hospital
3	(J. E.) Colored Male 45	Ulcerocaseous pulmonary tuberculosis	12/23/26	—	—	75	.....	Had been sick presumably only about 3 months before admission to the hospital. Pulse rate varied from 84 to 128; respirations, 22 to 32; temperature, 97.6 to 103.4 F. Had an afternoon elevation of temperature regularly. He was well developed and muscular but looked acutely ill. No tubercle bacilli found in sputum. Roentgen-ray observations: ulcerocaseous pulmonary tuberculosis involving both upper lobes, with a large cavity in left upper lobe near vertebral column. Patient died 1/7/27, after 5 weeks in hospital. Necropsy observations: extensive ulcerative and caseous bronchopneumonic tuberculosis of both lungs
4	(F. R.) Colored Male 44	Pulmonary tuberculosis	12/23/26	—	—	70	.....	Cough for 5 months prior to admission. Was considered to have a mild, doubtful case, but later became worse. Did not seem acutely ill at the time of the test and was allowed to walk around the ward at that time. Pulse rate varied from 60 to 72; respirations, 22 to 30; temperature, 97 to 102. Urine, negative. Tubercle bacilli in sputum. Roentgen-ray observations: ulcerocaseous pulmonary tuberculosis inviolving the upper two thirds of left and upper one half of right lung. Patient died on 4/4/27, after 5½ months in the hospital
5	(G. A.) Colored Male 46	Far advanced pulmonary tuberculosis	3/14/27	—	—	60	Forearms cold	Contracted a cold about a year before admission. Since then weakness and loss of weight of 35 pounds (15.9 Kg.). Had cough for a few months. Irregular temperature up to 3/12/27, and after that a constantly subnormal temperature. Pulse comparatively high. Patient died 3/14/27 after almost 2 months in the hospital
6	(P. C.) Mexican Male 33	Pulmonary tuberculosis	3/18/27	—	—	50 to 55	.....	Cough and night sweats for 1 month prior to admission. Anorexia and general weakness. Loss of weight of 10 pounds (4.5 Kg.) in 1 month. No hemoptysis. Slight cervical adenopathy bilaterally. Urinalysis negative. Tubercle bacilli in sputum. Roentgen-ray observations: an irregular mottling in both sides of chest; an increase in hilum shadows believed to be of tuberculous origin. Small multiple cavities appeared to be present on right side. Patient died 6/6/27, after 5½ months in the hospital

7	(G. W.) Colored Male 39	Far advanced pulmonary tuberculosis	3/ 5/27 3/ 8/27 3/10/27	— — —	— — —	45 49 46	Patient at ease Patient at ease, not having a high temperature in last 3 days	Presumably well until 1 month before admission, when he contracted a cold with cough and expectoration. Pulse rate varied from 78 to 124; respirations, 24 to 36. The temperature was subnormal most of the time. No tubercle bacilli found in sputum. Roentgen-ray observations: density increased with slight trabeculated appearance from right apex to fifth rib. Was considered as having an arrested case on discharge on 4/7/27, after 5 weeks in the hospital
8	(H. C.) Colored Male 57	Far advanced pulmonary tuberculosis; senile arteriosclerosis; myocarditis; ancient right sided hemiplegia; syphilis	3/18/27	—	—	45	.....	Contracted a cold last October and gradually lost weight, 15 pounds (6.8 Kg.) since then. Expectoration for 5 years and a paralytic stroke 5 years ago. Had had a positive Wassermann reaction and antisyphilitic treatment. Skin was scaling. Urinalysis negative. No tubercle bacilli found in sputum. Roentgen-ray observations: pleural fibrosis and fluid extending from the right second rib to the diaphragm, obliterating right lateral border. Four small cavities present in right supraclavicular region, not accompanied, however, by tuberculous mottling. Was not considered as having a far advanced case at the time of the skin tests. Patient died 5/23/27, after 3 months in the hospital
9	(S. N.) Porto Rican Male 33	Far advanced pulmonary tuberculosis; ulcerocaseous and nodular; gastro-intestinal tuberculosis	1/27/27 3/ 3/27	— ..	— ..	35 25	..... Patient in serious condition	Had had recent hemorrhages when tested. Tubercle bacilli in sputum. Patient died 3/3/27, after 7 months in the hospital
10	(J. B.) White Male 44	Far advanced pulmonary tuberculosis	2/19/27 2/21/27	— ..	— ..	30 38	.....	Presumably sick for only 2 months prior to admission. Urinalysis negative. No tubercle bacilli found in sputum. Patient died 2/23/27, after 3 weeks in the hospital
11	(W. L.) Colored Male 28	Far advanced bilateral ulcerative pulmonary tuberculosis	1/10/27 1/12/27	— ..	— ..	31 30	..... Irrational; meningeal involvement?	Stated that he had been well up to 3 to 4 weeks before admission. Pulse rate went up to 144, respirations to 40 and the temperature to 104. Urinalysis: albumin, positive; sugar, negative. No tubercle bacilli found in sputum. Patient died 1/13/27, after 11 days in the hospital
12	(F. R.) Colored Male 20	Far advanced pulmonary tuberculosis	4/ 6/27 4/ 7/27 4/ 8/27 4/11/27 4/15/27	— — — — —	— — + ++ ++	30 27 30 30 25	..... Left leg swollen Unable to talk	On admission complained of cough, 1 month; weakness, 2 months; loss of weight of 15 to 20 pounds (6.8 to 9.0 Kg.) in 2 months, and night sweats, 2 months. Was acutely ill, greatly emaciated and very weak. Physicial observations were those of advanced tuberculosis. Temperature varied from 98 to 104.6 F., pulse rate from 88 to 144, respirations from 26 to 48. Urinalysis: albumin, positive; sugar, negative. No tubercle bacilli found in sputum. Patient died 4/16/27, after 2 weeks in the hospital

> = more than; ± = about; + = present; — = absent.

Results of Injection of Intradermal Salt Solution Test on Twenty-Nine Tuberculous Patients—Continued

Case	Initials Race Sex Age	Diagnosis	Date of Skin Tests	Edema		Disappearance Time in Minutes in Forearm	Comment	Clinical Notes
				Arms	Legs			
13	(D. B.) Colored Male 33	Moderately advanced pulmonary tuberculosis with far advanced genito-urinary tuberculosis	12/26/26	—	—	28 to 30	.....	Had one tuberculous testicle removed about 3 to 4 years ago. Many discharging sinuses with extravasation of urine in the lower part of the abdomen. Urinalysis: albumin, positive; blood, positive. Tubercle bacilli in sputum. Typical history and observations of pulmonary tuberculosis. Had a persistently low temperature in the last 8 days of life. Patient died on 1/8/27, after 7 weeks in the hospital
14	(T. M.) White Male 29	Far advanced pulmonary tuberculosis	3/ 5/27	—	—	25 to 30	.....	History very much like that in gastric ulcer. On roentgen-ray examination pulmonary tuberculosis was discovered and was confirmed by sputum examination. Considerable emaciation and a high temperature from time to time. Urinalysis negative. Roentgen-ray observations on 1/3/27; ulcerocaseous pulmonary tuberculosis with multiple cavity formation involving both upper lobes. Patient died 3/7/27, after 5 weeks in the tuberculosis hospital
15	(G. W.) White Male 38	Far advanced pulmonary tuberculosis	4/ 7/27	—	—	20	.....	Caught a "cold" last July in a hospital. On admission had had a cough for 3 months; loss of weight of 40 pounds (18.1 Kg.) in 3 months; pain in the chest, and hemoptysis for 1 month. Temperature varied from 98 to 102 F.; pulse rate from 92 to 116, respirations from 24 to 36. Urinalysis negative. No tubercle bacilli found in sputum. The disease evidently took a very rapid turn for the worse in the last few days of life. Patient died 4/16/27, after 13 days in the hospital
			4/ 8/27	—	—	30		
			4/ 9/27	—	—	45		
			4/13/27	—	—	23	Somewhat yellow; lips, gums and conjunctiva very pale	
			4/15/27	—	—	28	Looks very pale	
16	(J. L.) Colored Male 28	Far advanced pulmonary tuberculosis; tuberculous peritonitis	2/23/27	—	—	25	.....	On admission, had fluid in abdomen and was acutely ill. Temperature varied from normal to 104 F.; pulse rate from 92 to 128, respirations from 20 to 40. Urinalysis negative. Blood chemistry: total nonprotein nitrogen, 48 mg.; creatinine, 1.9 mg.; uric acid, 2.7 mg.; sodium chloride, 0.52 per cent; cholesterol, 0.148 per cent on 2/4/27. No tubercle bacilli found in sputum. Patient died 2/28/27, after 5 weeks in the hospital
			2/24/27	..	..	25		
			2/26/27	..	..	15		
17	(E. L.) Colored Male 23	Far advanced pulmonary tuberculosis; empyema; draining sinuses in left lower axillary space	12/20/26	—	—	18 to 20	.....	A rather thin colored man with a history of empyema of 8 months' duration. During January developed edema, first of the right leg, then of the left leg and the scrotum, it became generalized in the last few days of life. Tubercle bacilli in sputum. Patient died 2/21/27
			1/10/27	—	—	23		
			1/20/27	—	+	33	No elevation of afternoon temperature	
18	(J. D.) White Male 39	Far advanced pulmonary tuberculosis; alcoholism	1/13/27	—	—	20	.....	An emaciated, acutely ill person. History of tuberculosis for 8 years and chronic alcoholism. Urinalysis negative. Blood chemistry: total nonprotein nitrogen, 30 mg.; uric acid, 2 mg.; sodium chloride, 0.45 per cent; carbon dioxide capacity, 49 on 1/13/27. No tubercle bacilli found in sputum. Patient died 1/19/27, after 2 weeks in the hospital
			1/14/27	..	..	20		
			1/15/27	..	..	25		

19	(L. K.) Colored Male 23	Far advanced pulmonary tuberculosis; tuberculosis of wrist	1/19/27 1/20/27	— ..	— ..	20 14	....	Contracted a cold about 4 months before admission. Typical history and observations of pulmonary tuberculosis with a high temperature and pulse rate most of the time. Urinalysis negative. No tubercle bacilli found in sputum. Patient died 2/4/27, after 3 weeks in the hospital
20	(W. M.) Colored Male 31	Far advanced pulmonary tuberculosis with cavitation	1/27/27 1/31/27 2/ 2/27 2/ 3/27 2/ 4/27	— — —	— — —	20 to 25 15 20± 18± 20 to 22	..... Irrational Looks brighter Looks brighter	Knowledge of tuberculosis for 3 years and cough and expectoration for 3 months. Greatly emaciated with quite regularly an afternoon elevation of temperature as high as 102.2. Pulse rate rapid most of the time, as high as 132; respirations from 22 to 32. Blood chemistry: total nonprotein nitrogen, 33 mg.; creatinine, 1.4 mg.; uric acid, 2.1 mg.; sodium chloride, 0.48 per cent; cholesterol, 0.125 per cent; carbon dioxide capacity, 21 on 1/31/27. No tubercle bacilli found in sputum. Patient died 2/7/27, after 2½ weeks in the hospital
21	(L. L.) Colored Male 29	Far advanced pulmonary tuberculosis	1/10/27 1/11/27 1/12/27	—	—	14 15 13	..... Irrational; dyspneic Dyspneic	History of cough of from 9 to 10 months' duration and hemoptysis twice in the last 8 months. Classical history and physical observations of tuberculosis. Urinalysis negative. Tubercle bacilli found in sputum. Patient died 1/12/27, after 2 weeks in the hospital
22	(Y. P.) Colored Male 19	Far advanced bilateral pulmonary tuberculosis	2/23/27 2/24/27 2/26/27	— — —	— — —	13 15 10	Patient toxic ..... Unchanged In serious condition	Sick only 4 months when he entered the hospital. Had lost about 50 pounds (22.7 Kg.) and had been hoarse for about 2 weeks. Pulse rate varied from 100 to 134, respirations from 32 to 54, temperature from 96.6 to 101.8 F. Was acutely ill. No tubercle bacilli found in sputum. Patient died 2/26/27, after 9 days in the hospital
23	(L. E.) White Female About 40	Far advanced pulmonary tuberculosis	1/13/27	..	..	12	.....	An emaciated white woman with thin arms. History of a cough of 1½ years' duration and sore throat and aphonia for 8 weeks. Tubercle bacilli in sputum. Patient died 1/15/27, after 4 days in the hospital
24	(B. D.) Colored Male 24	Far advanced pulmonary tuberculosis with draining appendiceal scar sinus	1/19/27 1/20/27	— ..	— ..	10 21	....	An emaciated man with a peeling skin and very little subcutaneous fat. Presumably well up to August, 1926, when he had an appendectomy. Urinalysis negative. Tubercle bacilli in sputum. Patient died 1/20/27, after 8 days in the hospital
25	(A. M.) White Male 15	Miliary tuberculosis; acute disseminated tuberculosis; tuberculosis of second lumbar spine	12/23/26	—	—	30	.....	History of a previous injury to the spine. A thin, emaciated white boy, who looked cyanotic and acutely ill but was rational. Roentgen-ray observations: tuberculous spondylitis, miliary tuberculosis of both lungs. Died 12/23/26, after a month in the hospital

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Results of Injection of Intradermal Salt Solution Test on Twenty-Nine Tuberculous Patients—Continued

Case	Initials Race Sex Age	Diagnosis	Date of Skin Tests	Edema		Disappearance Time in Minutes in Forearm	Comment	Clinical Notes
				Arms	Legs			
26	(J. G.) Mexican Male 25	Miliary tuberculosis	2/ 2/27 2/ 3/27 2/ 4/27	—	—	20 20 20	.....	Well until 1/13/27. On admission complained of cough, fever, anorexia, hoarseness. Was dyspneic. Roentgen-ray observations: flecked markings throughout lung fields, presumably miliary tuberculosis. Wassermann test negative. White blood cells, 3,200 (1/23/27). White blood cells, 4,100; polymorphonuclears, 73 per cent; lymphocytes, 24 per cent (1/30/27). Blood chemistry: total nonprotein nitrogen, 33.3 mg.; urea nitrogen, 16 mg.; uric acid, 1.8 mg.; sodium chloride, 0.39 per cent; cholesterol, 0.125 per cent; carbon dioxide capacity, 57 (2/4/27). Widal test negative. No tubercle bacilli found in sputum. Died 2/7/27 after 2 weeks in the hospital
27	(F. K.) Colored Female 46	Bilateral pulmonary tuberculosis; tuberculous peritonitis	11/30/26	—	—	40	.....	History of abdominal pain and swelling for 7 months; cough, 3 weeks, and marked loss of weight. In past history, moderate alcoholism and probable syphilis. Had chest symptoms which suggested tuberculosis, and a distended abdomen. Septic afternoon temperature in the first two weeks. Much improved on discharge, 12/28/26, after 5 weeks in the hospital, having had normal temperature for several days. Urine negative. Blood pressure 110/60. Wassermann 4 plus. Blood chemistry normal. No tubercle bacilli found in sputum
28	(E. H.) Colored Male 33	Tuberculous peritonitis	12/ 7/26 12/10/26 12/14/26 12/15/26 12/16/26 12/18/26	—	—	40 30 18 18 to 20 18 20 to 25	.....	History of pain and swelling of abdomen, 3 weeks; chills, fever and sweats, 5 weeks, and considerable loss of weight. The observations were distended abdomen, liver and spleen not palpable following an abdominal paracentesis in which 3,000 cc. of fluid of specific gravity 1.020 were removed. Had septic afternoon temperature, with rapid pulse and respiration. Urinalysis: albumin, trace; sugar, negative; pus cells, positive; granular casts, few. Blood pressure, 100/60; hemoglobin, 80 per cent; red blood cells, 4,750,000; white blood cells, 4,650. Smear of paracentesis fluid showed a predominance of lymphocytes. Was discharged with condition unchanged 12/29/26, after 4 weeks in the hospital
29	(E. R.) White Male 52	Chronic ulcerative tuberculosis of right apex with cavity; hypostatic pneumonia; cirrhosis of liver with ascites; terminal generalized miliary tuberculosis	11/16/26 11/17/26	— ..	+ ..	2 to 3 1	Abdomen tapped, 10,600 cc. of yellow fluid removed; specific gravity 1.012	On admission looked cyanotic, drowsy, and was rolling eyes as if moribund. History of loss of 30 pounds (13.6 Kg.) in weight, weakness and gastro-intestinal distress in the last 4 months; swelling of abdomen in the last 2 months. Past history: chancre 20 years ago, gonorrhea several times, epilepsy and alcoholism. Observations: dulness in lungs, swollen abdomen, edema of ankles and lower part of legs, greatly emaciated arms. Urinalysis negative. Blood chemistry negative. Blood pressure 98/80. Wassermann negative. Tubercle bacilli in sputum. Died 11/18/26, after 5 days in the hospital. Necropsy observations: generalized miliary tuberculosis of lungs, liver, spleen, kidneys, and mesenteric and abdominal lymph glands. Extreme ulcerocaseous tuberculosis of lungs, ileum and urinary bladder; atrophic cirrhosis of liver; hydrothorax; hydroperitoneum

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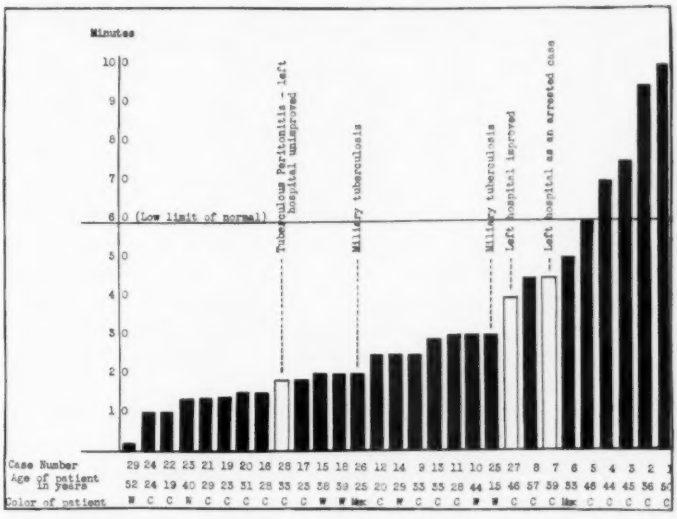
condition diagnosed as pulmonary tuberculosis; two had miliary tuberculosis; one, an acute miliary tuberculosis terminating in ulcerative pulmonary tuberculosis, and one, tuberculous peritonitis. All except three died while in the hospital, two were discharged improved and one unimproved. Edema was not palpable in the arm in any case; it was found in only three cases in the leg. The results of the tests and the clinical data are given in the table and are shown in the chart which was constructed from data taken from the table.

It is seen that in this group of patients with advanced tuberculosis, the disappearance time is usually markedly low. In sixteen patients, the time was only twenty-five minutes or less; most of them showed symp-


Minutes
10 0
9 0
8 0
7 0
6 0 (Low limit of normal)
5 0
4 0
3 0
2 0
1 0
Tuberculous Peritonitis - left hospital unimproved
Miliary tuberculosis
Miliary tuberculosis
Left hospital improved
Left hospital as an arrested case
Case Number 29 24 22 23 21 19 20 16 28 17 15 18 26 12 14 9 13 11 10 25 27 8 7 6 5 4 3 2 1
Age of patient in years 52 24 19 40 29 23 51 28 33 25 36 39 25 20 29 33 33 28 44 15 46 57 39 33 46 44 45 36 5
Color of patient W C C W C C C C C C W W Mex C W C C C W W C C C Mex C C C C C

The heights of the columns represent the variations in the shortest time required for elevations caused by the injection of salt solution into the forearm to disappear in twenty-nine cases of tuberculosis. The black columns represent the patients who died in the hospital and the white columns those who were discharged. *W* indicates the white patients; *C*, the colored, and Mex, the Mexican.

toms of being toxic; some were irrational. One was a young Mexican man with a typical clinical and roentgen-ray picture of miliary tuberculosis. Although most of these patients showed a marked rise in temperature, pulse and respiration rate, a close relationship between these factors and the short disappearance time was not evident. Edema did not occur in the arms in any of these patients; in only two (cases 12 and 28) was there evidence pointing to involvement of the urinary

tract. Many of these patients were greatly emaciated, which naturally suggested that this loss of tissue might perhaps account for the short disappearance time. However, this explanation seems to be inadequate, since the disappearance time was long in some greatly emaciated individuals.

The results did not vary a great deal in the few patients on whom the tests were carried out both in the forearm and in the leg.

That tuberculosis does not necessarily lead to a low disappearance time can be readily seen from the chart. Of the eight patients that showed a disappearance time of forty-five minutes or more, three (cases 4, 6 and 7) were considered to have mild cases at the time of the tests; two of them died several months later. Two patients (cases 3 and 8), although seriously ill at the time of the tests, were not considered as having far advanced cases; one of these, however, died two weeks later. The remaining three (cases 1, 2 and 5) had only a few more days to live, although they gave histories of short duration of illness. It is worthy of note that these three patients with the longest disappearance times seemed to show little temperature reaction. The one who had the highest disappearance time in the entire series (one hour and fifty minutes) had a persistently subnormal temperature ranging between 96.2 F. and 97.6 F. In these three patients, the forearms were observed to be cold when exposed for a short time. All were greatly emaciated, which tends to show that emaciation alone is not sufficient to explain the low results obtained in the larger number of cases; furthermore, the young Mexican with a typical picture of miliary tuberculosis and a disappearance time of twenty minutes was not emaciated.

The remaining five patients in different states of the disease gave results varying from twenty-eight to forty minutes.

Since most of the patients tested were negroes the low results are of enhanced significance, because the normal disappearance time has been shown Lash [5] to be considerably higher in negro women than in white women.

SUMMARY

The intradermal salt solution test was performed on twenty-six patients with pulmonary tuberculosis, two with miliary tuberculosis, one with pulmonary and acute miliary tuberculosis, and one with tuberculous peritonitis. In twenty-four of the twenty-nine patients the disappearance time of the elevation caused by the injection fell below the lower limit of normal, and in most of these it was greatly below normal.

In general, the shortest times were obtained in patients with symptoms of toxicity, who in many instances had a septic type of temperature. Extended disappearance time was usually noted in patients with a tendency to subnormal temperature.

That pulmonary tuberculosis does not always cause a markedly short disappearance time is shown by the observation of a disappearance time of sixty minutes or more in five patients, four of whom died within fifteen days after the time of the tests.

The possibility that secondary infection may have played an important part in causing the short disappearance times in these tuberculous patients must be considered.

COUNCILMANIA TENUIS AND C. DISSIMILIS, INTESTINAL AMEBAS OF MAN

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The detection of distinguishing structural features that may be relied on to separate the species of amebas, especially of the parasitic amebas in the digestive tract of mammals, is fraught with difficulties. These arise from changes in form in the motile phases due to locomotion, to the extrusion and retraction of pseudopodia, to the presence of cytoplasmic inclusions and to the modifications incident on changes in temperature and in hydrogen ion concentration. For example, a slight increase in acidity, as from p_H 7.0 to 5.8, markedly increases the locomotor activity and tends to elongate the pseudopodia.

In stained preparations of motile stages, the form of the body and of the pseudopodia is subject to changes due to contraction in smearing and fixation.

In the encysted stages, many of these modifications are eliminated, but others arise which disturb the uniformity of structure. Among these are the volume, number, distribution and time of occurrence of the glycogen vacuoles that determine the appearance of the cytoplasm, modify the location of nuclei and determine the numbers and location of the chromatoidals.

A second cytoplasmic constitutent is the chromatoidal substance organized in characteristic chromatoidal bodies that appear on the periphery of the glycogen vacuoles as the latter fade out, in the form of siderophil bodies which in turn decrease in number and finally fade out entirely with increase in the number of nuclei and aging of the cyst. These bodies have a characteristic range in size, shape and relative number in the different species of amebas. They vary greatly, however, within the species in these particulars, both with age and in different infections, probably as a result of either environmental influences or genetic or racial differences. There are stools and hosts in which chromatoidal-rich or chromatoidal-poor cysts are found that have a different appearance from each other because of the differences in the total and relative masses of chromatoidal substance and number of chromatoidal bodies. The form of these chromatoidal bodies is sometimes suggestive of liquid crystals with evidence of angular or semiangular facets. These structural features of the chromatoidals change with their increase in size, their coalescence and their solution and fading out. Although varying greatly in size, shape and proportions, they nevertheless exhibit similarities within the species which are somewhat characteristic.

The nuclei also vary in shape, structure, number, size and location, as mitosis proceeds and the increase from 1 to 2, 4, 8, or 16 as nuclear divisions end and the cyst comes to a state of nuclear equilibrium. The number of divisions is, in the main, characteristic for each species. Thus in *Iodamoeba bütschlii*, the completed number of nuclei in the cyst is rarely more than one; in *Endamoeba dysenteriae*, it is never more than four; in *Councilmania lafleuri* and *Endamoeba coli*, it is eight or sixteen, rarely thirty-two in the former. In *C. muris* and *C. decumani*, the maximum number is eight.

During the mitotic process the nuclei go through a succession of orderly changes in size and shape. The single nucleus of the cyst when first formed is much larger than those of the terminal stage. As each nucleus goes through mitosis, it first elongates into a broad spindle-shaped body, then constricts equatorially and greatly elongates; it parts in the middle, and each end reshapes itself into a sphere, with profound changes in internal structure during this process.

The number of the chromosomes is a characteristic of plants and animals, including amebas. The numbers and sizes of the chromosomes are basic, together with the siderophil substance forming the centrosomes at the apexes of the spindle, in determining the structure and appearance of the nucleus, not only at mitosis, but in the resting stage. The nucleus in the so-called resting stage of amebas in general thus comes to be one of the most reliable of all characters utilizable as a basis for classification and for diagnosis of species in intestinal infections. The number of chromosomes is to be detected only at, or near, the metaphase of mitosis; it is detected in relatively few infected stools, and requires skill and infinite patience to unravel, but is of greatest classificatory value in conjunction with other characteristics. Thus an ameba having about twenty chromosomes such as *Karyamoebina falcata* can not possibly be the same species as *Endamoeba dysenteriae* with only six chromosomes, as Wenyon [1] suggested.

For routine diagnosis and as a rule in specific determinations of the intestinal amebic fauna, one must make a great deal of use of the structure of the nuclei in the cysts, but nuclei utilized for this purpose are best studied when in a state of equilibrium with the mitotic divisions completed and metabolism in the cell, such as that involved in the glycogen-chromatoidal cycle, eliminated or at a low ebb. In such completed cysts, the maximum degree of uniformity of structure may be expected. There is even some variation in the total amount of chromatin, so that some "races" or cysts from some stools or hosts are much poorer in chromatin than others. Even with such differences, the

1. Wenyon, C. M.: Protozoology. A Manual for Medical Men, Veterinarian Zoologists, London, Ballière, Tindall and Cox, 1926, p. 209.

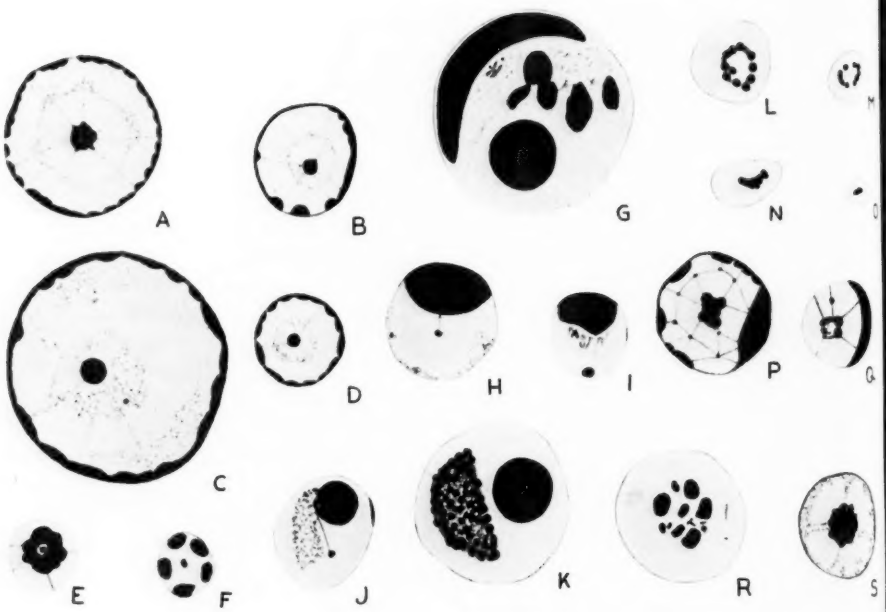

Fig. 1.—Comparative view of the nuclei of human intestinal amebae from fecal smears fixed in Schaudinn's fluid and stained in iron hematoxylin; × 4667.

EXPLANATION OF FIGURE 1

A, Endamoeba dysenteriae (Councilman and Lafleur) from a motile ameba in dysenteric stool, showing distributed peripheral chromatin, spoke radii, wide clear halo, and central, solid, spherical karyosome.

B, Endamoeba dysenteriae from a four-nucleated cyst, showing smaller size but similar structure, except that the karyosome is somewhat eccentric.

C, Endamoeba coli (Loesch) from a mononucleated cyst, showing distributed peripheral chromatin, spoke radii, small halo, and slightly eccentric, solid, spherical karyosome.

D, Endamoeba coli from an eight-nucleated cyst, showing similar structure.

E, Dientamoeba fragilis (Jepps and Dobell) from motile phase, showing no peripheral chromatin, nuclear membrane faint, large granules massed in large central karyosome and spoke radii to membrane.

F, Dientamoeba fragilis showing karyosome granules scattered toward periphery.

G, Karyamoebina falcata (Kofoid and Swezy) from a motile phase showing nuclear membrane free from peripheral chromatin except for one large crescentic blob, one large, solid, eccentric, spherical karyosome in clear halo, and some scattered chromatin blocks. Spoke radii are not present.

H, Endolimax nana (Wenyon and O'Connor) Brug, from a mononucleated cyst showing very faint nuclear membranes, one massive, lateral, lenticular blob of chromatin, minute centrosome on stalk which is the forming intradesmose; no spoke radii, and no halo.

I, Endolimax nana from a smaller mononucleated cyst showing intradesmose more extended, chromosomes forming in a crescent adjacent to the blob and movement of blob along intradesmose.

J, Iodamoeba bütschlii (Prowazek) Dobell from a mononucleated cyst showing faint nuclear membrane with no film of peripheral chromatin, a massive, lenticular, lateral blob and small centrosomes on stalk (the intradesmose) from blob, no halo and no spoke radii.

K, Iodamoeba bütschlii from another mononucleated cyst showing similar structure except that the crescentic mass of chromatin granules is more in evidence. This is the chromatin net from which the chromosomes will form.

L, Councilmania tenuis (Kuenen and Swellengrebel) Kofoid from a mononucleated cyst showing deformation of nuclear membrane, lack of peripheral chromatin and central karyosome dispersed in a ring-shaped group of large granules, no spoke radii nor halo.

M, Councilmania tenuis from a four-nucleated cyst with spherical nucleus and similar structure.

N, Councilmania tenuis from a four-nucleated cyst with karyosome granules massed in a central crescentic mass.

O, Councilmania tenuis from an eight-nucleated cyst with deformed nuclear membrane and minute granules massed in an elongated central karyosome.

P, Councilmania dissimilis sp. nov. from a motile ameba in culture showing scattered peripheral chromatin and large crescentic lateral blob (oblique to plane of focus), central karyosome composed of a group of discrete granules, spoke radii, and an intermediate zone of granules.

Q, Councilmania dissimilis from an eight-nucleated cyst showing lateral blob, dispersed central karyosome and spoke radii.

R, Councilmania lafleuri (Kofoid and Swezy) from an eight-nucleated cyst showing faint nuclear membrane with no peripheral chromatin and dispersed granules of the central karyosome.

S, Councilmania lafleuri from a different eight-nucleated cyst with small amount of faintly stained peripheral chromatin, spoke radii, and central spheroidal mass of discrete granules forming the karyosome.

microscopist may train himself to detect, with a high degree of accuracy, the specific distinctions between the cysts of the various amebas of the digestive tract of man.

The structure of the resting nucleus in mature cysts is thus the most available and at the same time the most critical morphologic criterion of the generic and specific distinctions among the intestinal amebas of man and other mammals.

It was on this basis of the structure of the resting nucleus that Kofoid and Swezy,[2] in part, distinguished the genus *Councilmania*, parasitica, in man. Later the species in rodents were assigned to it by Kessel[3] and Kofoid, Swezy and Kessel.[4] The striking differences in this nuclear structure as seen in the resting nucleus of the mature cysts of the different species of human intestinal amebas is shown in figure 1.

In the course of our investigation on the human intestinal *Protozoa* during the past years, we have become increasingly certain that there are two additional parasitic intestinal amebas of rather frequent occurrence in man, which are at present masquerading under the cover of other better known species. Both have distinct morphologic characteristics, and infections caused by them have typical pictures of occurrence, recurrence and distribution.

The first of these was originally described by Kuenen and Swellengrebel[5] as *Entamoeba tenuis* from man. According to them, its cysts are sometimes asymmetrical, and the nuclear membranes in the cysts are devoid of peripheral chromatin in distinct blobs, although the line representing this membrane is drawn by them as a heavy one. The nuclei are characteristically deformed, off the sphere, in all of their figures. The chromatoidals are rather small, rounded or rodlike. Cysts with one, two and four nuclei are figured. The nucleus has a halo and rather irregularly shaped subcentral or central karyosome.

We have long recognized this ameba in our routine laboratory examinations of stools, noting it on our laboratory records as "little *Councilmania*," but not reporting it, as we were uncertain of its status. It stains faintly, is easily confused, because of its size, and its ellipsoidal

2. Kofoid, C. A., and Swezy, O.: On the Free, Encysted and Budding Stages of Councilmania lafleuri, a Parasitic Amoeba of the Human Intestine, Univ. Calif. Pub. Zool. **20**:169, 1923.

3. Kessel, J. F.: The Distinguishing Characteristics of the Parasitic Amoebae of Culture Rats and Mice, Univ. Calif. Pub. Zool. **20**:489, 1924.

4. Kofoid, C. A.; Swezy, O., and Kessel, J. F.: On the Genus Councilmania, Budding Intestinal Amoebae Parasitic in Man and Rodents, Univ. Calif. Pub. Zool. **20**:431, 1923.

5. Kuenen, W. A., and Swellengrebel, N. H.: Korte beshrivjving van enkele minder bekende proyozoën nit den menschlijken darm, Nederl. Tijdschr. v. Geneesk. **57**:496, 1917.

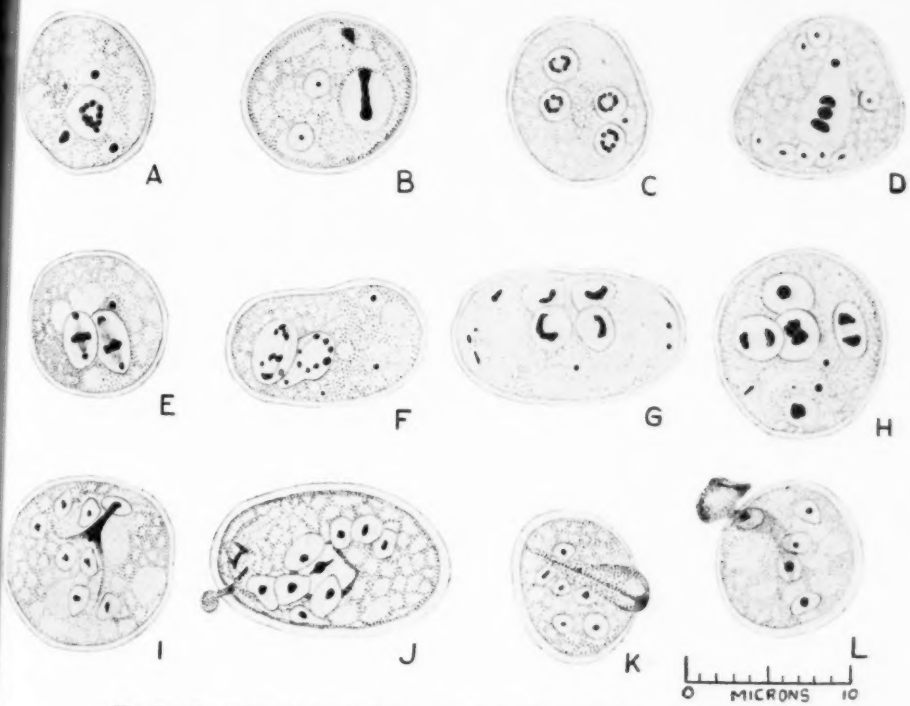

Fig. 2.—Councilmania tenuis (Kuenen and Swellengrebel) from a stained fecal smear from man from nine different cases; × 2,500.

A, mononucleated cyst with diffuse glycogen vacuoles, three subspheroidal chromatoidals in halo, subspherical nucleus with faint membrane, no peripheral chromatin and dispersed karyosome, probably a prophase.

B, binucleated cyst with diffuse glycogen vacuoles, two chromatoidals, one rod-shaped in halo, and nuclei with condensed karyosomes.

C, four-nucleated cyst, little evidence of glycogen vacuoles, one small chromatoidal, and nuclei with dispersed ring-shaped karyosomes.

D, eight-nucleated cyst with three chromatoidals in one halo, and remnants of a glycogen vacuole but quite asymmetrical karyosomes.

E, binucleated cyst with nuclei at metaphase of mitosis, diffuse glycogen vacuoles, and one chromatoidal.

F, binucleated cyst with little evidence of glycogen vacuoles; three small remnants of chromatoidals and nuclei in early anaphase with about six chromosomes.

G, four-nucleated cyst with little evidence of glycogen vacuoles, scattered chromatoidal remnants and nuclei with crescentic karyosomes.

H, four-nucleated cyst with little evidence of glycogen vacuoles, five chromatoidals and nuclei all in the anaphase with chromosomes massed at the poles of the intranuclear spindles.

I, eight-nucleated cyst with deformed nuclear membranes, irregular karyosomes, and several large glycogen vacuoles. Faint chromophil strands lead to the pore on the upper side from which the chromophil bud emerges.

J, eight-nucleated cyst with deformed nuclear membranes, and irregular karyosomes. The remnant of a chromatoidal lies in the center of a dark-bordered halo. A small cytoplasmic bud is emerging from the pore.

K, six-nucleated cyst with cytoplasm emerging from pore. Probably one amebula has already escaped.

L, five-nucleated cyst with cytoplasm emerging and one nucleus at the pore. Probably three amebulas have already escaped.

or asymmetrical cysts, with *Endolimax nana,* and, when spherical or viewed on end as spherical, looks like a small four-nucleated *Endamoeba dysenteriae.* In fact, Nöller [6] placed it in the synonymy of *Entamoeba hartmanni* Prowazek, but his illustrations of that so-called species do not include any figures of Kuenen and Swellgrebel's *Entamoeba tenuis.* Morphologically, culturally and in its pathogenic capacity, *E. hartmanni,* in our opinion, is only a small, but frequent phase of *Endamoeba dysenteriae* and should not be given specific recognition.

It is different, however, with the species *tenuis,* which is distinguishable. We allocate it, however, to the genus *Councilmania* instead of *Endamoeba* (or *Entamoeba*), because of the structure of its nuclei in the matured cysts.

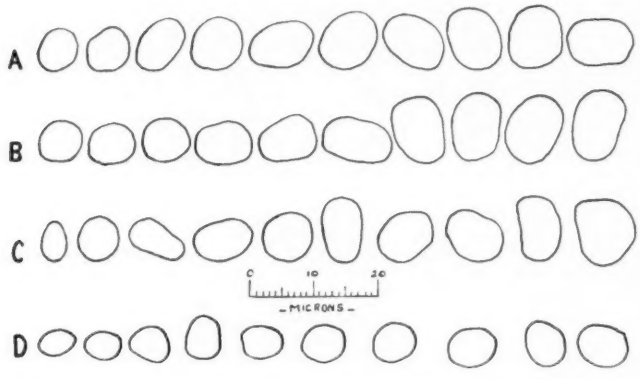

Fig. 3.—Cysts of Councilmania tenuis in outline from four different cases in man. Case A, average long and short diameters 6.5 and 5.2 microns; case B, 8.9 and 6.2; case C, 9.1 and 6.7; case D, 9.4 and 7.4. Average of the 40 cysts 8.5 by 6.4 microns; × 1,000.

COUNCILMANIA TENUIS

The following morphologic feature characterize this species: The motile stages of *Councilmania tenuis* (Kuenen and Swellengrebel [5]) are small, from 7 to 10 microns, with broadly rounded, clear pseudopodia, fairly active; encysted phases are abundant in stools with one nucleated and four nucleated stages predominating, less frequently eight nucleated. The cysts measure from 3.1 by 5.7 to 8 by 10.6 microns, the average mean diameter of 500 being 7.1 microns, generally slightly

6. Nöller, W.: Die wichtigsten parasitischen Protozoen des Menschen und der Tiere: I. Teil, Einführung un die allgemeine Kenntnis und die Untersuchung der parasitischen Protozoen und Abschnitt: I. Die parasitischen Rhizopoden, Berlin, Schoetz, 1922, p. 272.

off the sphere, ellipsoidal, ovate or asymmetrical to a slight degree. Glycogen is not massive, usually in several larger or numerous smaller not clearly delineated vacuoles. There are few chromatoidals, rather small, broadly ellipsoidal or ovoidal, often slightly asymmetrical or small, subspheroidal or irregular in a clear halo (of solution ?). The nuclei are very faint, difficult to locate and to define because of the lack of peripheral chromatin, often subspherical or with irregularities in contour, with central or subcentral, irregular, rather large deeply staining karyosome formed by an aggregate of small granules, clearly separable in many nuclei, with greater difficulty in others. As in *Councilmania lafleuri*, the karyosome may be subpheroidal, reniform, ring-shaped, or a semicircular row of heavy granules, but, as a general rule, under high magnification and good definition, it is seen to be an irregular aggregate of chromatin spherules. In many nuclei its granules are widely dispersed. At mitosis the karyosome moves to the periphery and it forms the typical, but faint, intradesmose as the chromosomes form, in part at least, from its substance. Their number is about six, but has not yet been accurately determined.

The cysts bud less freely than those of *C. lafleuri* in the stool and are found in this condition in fresh smears and stained slides. Nuclei have been found in transit through the minute hole in the cysts and in the budded amebula attached to, or adjacent to, the parent cyst.

Due to the fact that the cytoplasm of this species destains readily in iron hematoxylin, and that there is not any appreciable amount of chromatin on the nuclear membrane, the cysts of this ameba have a different aspect in stained fecal smears from those of other amebas such as *E. dysenteriae* with more stainable cytoplasm and nuclear wall encrusted with black peripheral chromatin. The facts that the chromatoidals are ovate or subspherical and often small, and that the central karyosomes are rather large and in clear halos not unlike those about the decreasing chromatoidals, add to the aberrant appearance of these amebic cysts. This may lead the examiner of the smear to throw them into the discard or to regard them merely as aberrant *Endolimax nana* or even *Endamoeba dysenteriae* of the smaller phases, from 7 to 9 microns, in which the amount of peripheral chromatin is not so noticeable as in the larger phases. The large size of the central karyosomes in some cysts and the faint nuclear membrane of *C. tenuis* also give a picture suggestively like that of the nuclei of chromatin-poor *Endolimax nana* seen with the lateral blobs in face view. The similarity is heightened by the subspherical shapes of some of the cysts of *C. tenuis*.

Nothing critical is known of the pathogenicity of this species. Animal experimentation and serologic tests with pure cultures as well as clinical study of cases of pure infections by this species are needed to establish its relations to its host.

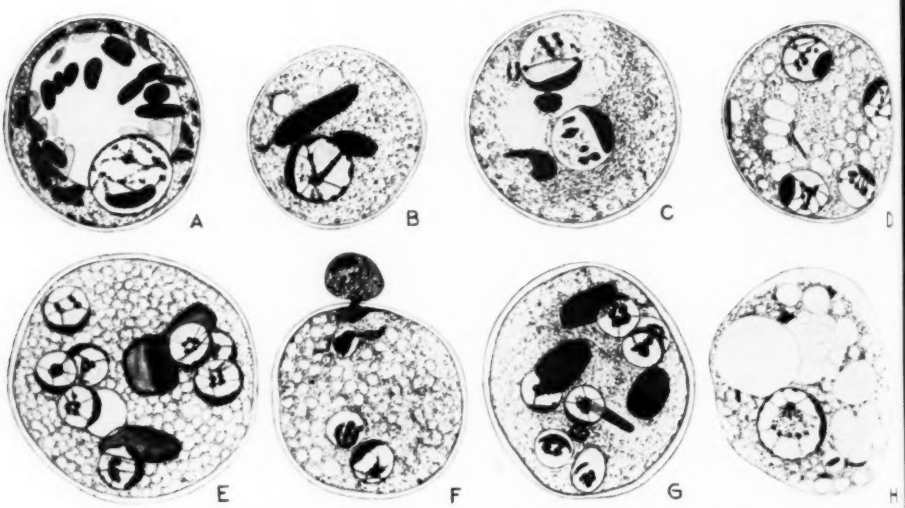

Fig. 4.—Councilmania dissimilis sp. nov. from fecal smears stained in iron hematoxylin; × 2210.

A, mononucleated cyst with large spheroidal (probably lenticular in the plane of the section) glycogen vacuole, numerous small faintly bordered chromatoidal bodies, nucleus in early prophase, with peripheral chromatin network and heavy lateral blob.

B, mononucleated cysts with two chromatoidals with asymmetrical ends, three small glycogen vacuoles, and nucleus with lateral blob, eccentric, irregular karyosome and radii.

C, binucleated cyst with disappearing diffuse lenticular eccentric glycogen vacuole; two small flakelike chromatoidals, nuclei in prophase with emerging chromosomes, the left with an intradesmose connected at one end with the lateral blob.

D, four-nucleated cyst with diffuse vacuolation, linear remnants of the chromatoidals, nuclei with heavy lateral blobs and dispersed karyosomes.

E, eight-nucleated cyst with diffuse vacuolation, and one small vacuole, stout, angled, bordered chromatoidals, nuclei with marked lateral blobs and dispersed karyosomes.

F, budding cyst with three nuclei, one in the escaping amebula and chromophil cytoplasm in pore and bud. Remnant of a chromatoidal in a halo, and several other minute remnants. Nuclei with lateral blobs and somewhat dispersed karyosomes.

G, cyst with seven nuclei with lateral blobs and variously dispersed karyosomes, four somewhat bordered squarish or rodlike chromatoidals, and no glycogen vacuole. The cytoplasm is chromophil toward and in a small circular pore on the upper surface. Probably one amebula has already escaped reducing the eight nuclei to seven.

H, motile ameba from fecal smear with retracted clear pseudopodia and nucleus with lateral blob and dispersed karyosome.

The incidence of infection by *Councilmania tenuis* in man is rather high. In 7,746 examinations of about 2,587 persons made in my laboratory between Jan. 1, 1927, and May 31, we recorded 239 cases, or about 9.2 per cent. Previous records in the last two years approximate this. This figures are slightly higher than is warranted by the real facts, as the number of persons is made up from our monthly totals and involves a small overlap.

The second species is one which masquerades under the cover of *Endamoeba dysenteriae,* which it resembles closely in many particulars. It is, indeed, included in some of the published figures of cysts of *E. dysenteriae,* as in those of Hartmann and Belar[7] (1921). It may be responsible for the belief that *E. dysenteriae* sometimes goes to the eight-nucleated stage in the cyst, and that this species sometimes exhibits the appearance of budding. It undoubtedly is being reported as *E. dysenteriae* for treatment. The extent to which its presence in man and its present confusion with *E. dysenteriae* (large race) complicates the clinical picture of amebiasis and of amebic therapy can be determined only by prolonged study. It is important that this species be recognized in examination of the stool and ruled out of possible confusion with the larger race of *E. dysenteriae,* especially by critical, clinical and therapeutic investigation and comparisons of cases of pure infections by the two species singly. The characters of this species of *Councilmania* are given in the following paragraphs.

COUNCILMANIA DISSIMILIS, SP. NOV.

The outstanding features of this species are: the heavy lateral blob of peripheral chromatin on the nuclear membranes, and the predominantly dispersed karyosomes in the matured cysts, the occurrence of eight-nucleated cysts and the free budding of cysts in the feces and in fresh untreated cultures.

The nucleus is typically spherical, but seems to be subject to slight deformations to a somewhat greater extent than in *E. dysenteriae* and to a smaller extent than in *E. gingivalis.* The nuclear membrane is faint, especially in cysts and in the chromatin-free parts of the wall. Its chromatin occurs in two regions, the peripheral, applied to the nuclear membrane, and the karyosomal or central, which usually is considerably dispersed.

The peripheral chromatin has a characteristic distribution. Instead of being distributed over the inner surface of the nuclear membrane in a thin layer, or scattered in small masses of subuniform or somewhat

7. Hartmann, M., and Belar, K.: Die parasitischen Amöben des Menschen und der Säugetiere, in Prowazek, S. von, and Nöller, W.: Handbuch der pathogenen Protozoen, Leipzig, Barth, 37 fig. in text, 1921, vol. 3, p. 1295.

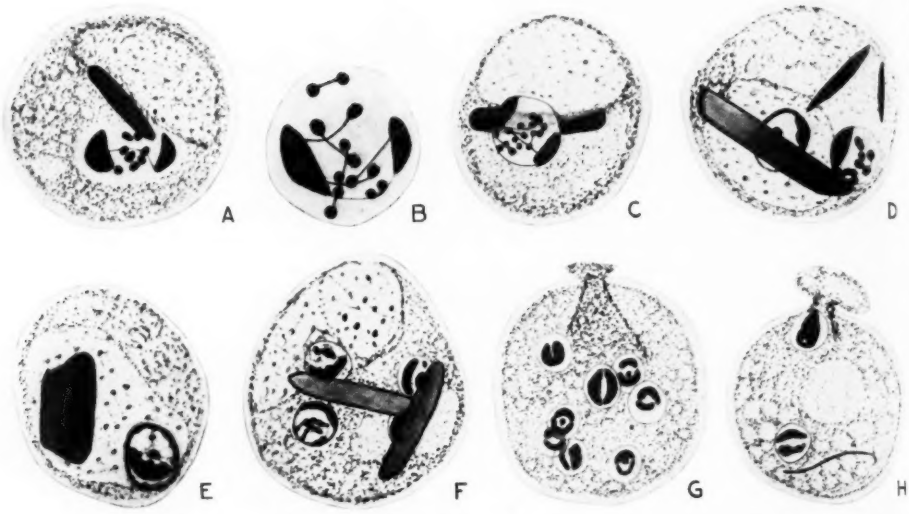

Fig. 5.—Cysts of councilmania dissimilis Kofoid from fecal smears. Reduced from a magnification × 2210. Drawings by Mrs. Dora Henry.

A, mononucleated cyst with large lateral asymmetrically lenticular glycogen vacuole with stained nodal network; nucleus in early metaphase with eight undivided chromosomes, and slender linear intradesmose joining two polar masses derived from the lateral blob of peripheral chromatin. Centrosomes, if present at the ends of the intradesmose, are not visible. A single rod-shaped chromatoidal with ends lies below the nucleus.

B, nucleus only, from another mononucleated cyst with more advanced stage of division of the chromosomes. Note the differences in size and state of division.

C, mononucleated cyst in more advanced stage of nuclear division than figures a and b. Slender intradesmose joins ends of the polar siderophil masses. Single lateral glycogen vacuole and single chromatoidal rod with squarish ends.

D, binucleated cyst with lateral glycogen vacuole, three chromatoidals, the largest with markedly asymmetrical subangular ends and deeply stained peripheral layer; nuclei with lateral blobs; chromosomes are visible in right nucleus.

E, mononucleated cyst with single flattened asymmetrical chromatoidal with subangular ends and dark peripheral layer. Large glycogen vacuole and nucleus with lateral blob and some chromatin in strands on the membrane are present.

F, four-nucleated cyst with two glycogen vacuoles, two rod-shaped chromatoidals with asymmetrical subangular ends and peripheral siderophil layer.

G, eight-nucleated cyst with chromophil cytoplasm emerging from pore.

H, binucleated cyst with amebula emerging. Compare size of nuclei with those in figure *g*. Probably the six amebulas have already escaped.

varying size, as it is in *E. dysenteriae*, it is found in *C. dissimilis* massed mainly, or almost wholly, in one large lateral blob. This single mass is crescentic in outline, and spans almost one half of the circumference of an optical section of a nucleus when the blob is in the plane of the section. It may appear shorter than this, but in such cases it will be found usually that it is foreshortened by the obliquity of its position with reference to the focal plane. Its greatest thickness ranges from 0.14 to 0.30 of the nuclear diameter, and its width is somewhat greater. It stains intensely black because of its mass. Its inner face may show evidence of indentation or subdivision. When it lies on the upper or lower surface of the nucleus, it may be overlooked.

In the relatively infrequent binucleated stage, the lateral blobs are reduced or even absent. In some nuclei, there may be small accumulations of peripheral chromatin elsewhere than in the blob, which appear in optical section as thin blobs or scattered granules applied to the nuclear membrane. In some instances in motile forms in culture, the blob is considerably reduced in thickness, and the peripheral extension of the chromatin is increased. The most striking feature of this species is the structure of the nucleus of the mature cyst with the heavy lateral blob and faint nuclear membrane elsewhere on the nuclear surface. In the binucleated stage, because of its close juxtaposition to the preceding and following mitosis, the lateral blob is less in evidence.

The central karyosome (fig. 4, D-H) is composed of a number of discrete granules which in the nuclei of the matured cyst are often rather widely dispersed. Evidence of a clear halo is not found around the karyosome as in *E. dysenteriae* (Kofoid and Swezy[8]) or of the typical spheroidal state of the karyosome so characteristic of *E. dysenteriae*. This dispersal is strikingly similar in pattern to that described for *Councilmania lafleuri* by Kofoid and Swezy (1921) and found by Kessel (1924) in *C. muris* and *C. decumani* from rats and mice.

The number of nuclei in the cyst depends on the age of the cysts. In some stools, mononucleated cysts with large nuclei are abundant, many in the prophases of mitosis. In others, four-nucleated cysts predominate with few mononucleates and binucleates. Less frequently, and generally in stools with mature four-nucleated cysts, a few cysts with eight nuclei occur. This number, as that of the four-nucleated cysts, is reduced by budding and the successive escape of amebulas with nuclei from the cyst in some instances. Four-nucleated cysts are frequently seen with prophases of mitosis in their nuclei.

We have never seen this increase in the number of nuclei from four to eight in the cysts in *Endamoeba dysenteriae*. The cases, stools and smears in which the eight-nucleated cysts occur in *C. dissimilis* are,

8. Kofoid and Swezy: 1924, plate 17, figs. 32-43.

however, so infrequent that this feature is available only occasionally for diagnostic purposes in examinations of stools. It is, however, of classificatory value as a mark of a distinct species.

The number of chromosomes in this species is eight. The chromosomes can be counted in the prophase as split, meridional, faintly stained structures on the nuclear membrane and at the late metaphase as bilobed or divided masses of unequal sizes. The material of the lateral blob forms around the polar centrosomes and perhaps contributes to the faint intradesmose joining them.

The glycogen vacuole is characteristically eccentric in location, best seen at its maximum development in mononucleated cysts, often contains throughout its entire area in stained cysts a fine reticulum with stained nodal granules, and may fill nearly one half of the cyst. It is asymmetrically lenticular in contour and crowds close to the periphery. It may be broken up into smaller areas of equal or varying size with somewhat diffuse margins, often larger in the periphery of the cyst. The lateral position of this vacuole is correlated with the crowding of the single nucleus to one side.

The chromatoidal substance typically stains a dense homogeneous black in iron hematoxylin, but in this species exhibits considerably more variability than in *E. dysenteriae*. Black bordered chromatoidal bodies with paler centers are frequent, and washed out pale bodies also occur but without borders. Likewise, there is rather more than the usual evidence of halos (or shrinkage?) about these bodies.

The shape and size of these bodies vary greatly according to the phase of their formation, either near the surface of the large glycogen vacuole in the early period of their history or as slender rods in halos of solution in their last stages. In the earliest phases they are oval or asymmetrically ellipsoidal in outline, not over 2 to 2.5 times as long as wide, rounded but more or less asymmetrical at the two ends and often flattened against the glycogen mass to a thickness half their width. There may be over forty such bodies crowded about the surface of the glycogen mass when it is large. The number present in later stages decreases rapidly, until in the four to eight nucleated stage there may be only from one to four present, and in the old cyst, none. When the glycogen and the chromatoidal substances are small in amount, and also as the cysts with much chromatoidal substances age, there is often only a small number or a single large chromatoidal body. The largest may be as long as the diameter of the cyst and 0.2 of the length in width, or short and stout, 0.5 as long as wide, or even squarish. In favorable views and probably in all cases, the two ends are asymmetrical and singly or doubly obliquely facetted with rounded angles. The squarish and rectangular types are usually flattened, the longer types more

rounded. Whatever the position, careful focusing often reveals this terminal asymmetry and angularity. Their last remnants are slender rods or irregular flakes.

The process of budding of the cysts occurs freely in the stool, as in *C. lafleuri*. Budding cysts are found in fresh smears not under the least external pressure, in stained smears, in cysts formed in culture tubes, and the process of the escape of the amebulas has been watched under the microscope. The pore through which the budding amebulas escape is from 0.35 to 0.50 the diameter of the nucleus of the four-nucleated cysts. The area of the cytoplasm leading toward the pore stains a little more deeply as though condensed, as may also that of the amebula outside of the wall of the cyst. This darker staining, as a rule, it not so marked as it is in *C. lafleuri*. Budding has been observed in cysts with one, four, and eight nuclei.

The cysts are rather uniformly close to the spherical form, whereas in *C. lafleuri* they tend somewhat more toward the broadly ellipsoidal

TABLE 1.—*Range and Diameter of Cysts in Cases of C. Dissimilis*

Number	Range	Average	Diameters of Extremes
29056	11.6 to 14.9	13.1	11.6 by 13.3
52260	11.6 to 14.9	13.4	14.9 by 19.2
63774	11.6 to 14.9	12.9	13.3 by 16.6
63885	13.3 to 16.6	14.4	11.6 by 16.6
71341	11.6 to 16.6	14.3	11.6 by 14.9

contour. The range and average diameter noted of ten cysts and the most extreme departure from the spherical in five different cases of *C. dissimilis* are given in table 1. The diameter used when the cyst was not exactly spherical was the longer one.

Councilmania dissimilis is less frequent in man than either *C. lafleuri* or *C. tenuis*. In 7,746 examinations of about 2,587 persons in my laboratory between January 1 and May 31, there were eleven cases of infection, or about 0.4 per cent. We have seen probably more than 100 cases. The cysts are often abundant in the stool; not infrequently as many as five cysts may be seen in a single oil immersion field, indicating unusually heavy infections. As in the cases of other intestinal infections, pure infections by this species alone are rare. It usually occurs with one or more of the other commoner *Protozoa*. It persists in varying frequency during any period of examination, and may decrease markedly or even disappear for a time, and then return in the stools.

The grounds for the specific separation of this ameba from *E. dysenteriae*, with which it is at present confused, are primarily the eight chromosomes as over against the six in that species, the distinctive large blob of chromatin, dispersed karyosome, eight nuclei in the cyst

and the frequency of budding in the stool. Clinical and cultural grounds are given in the following parts of this paper.

The grounds for placing the organism in the genus *Councilmania* are primarily the predominantly dispersed karyosome, a feature of nuclear structure in the resting nucleus of the matured cyst which characterizes all species of this genus. The slight tendency to asymmetry or off-the-sphere shape of the cyst, the frequent budding process in the stool and the chromophil condition associated with budding are also developed in the other species of this genus. In the genus *Endamoeba* (= *Entamoeba*), the karyosome is typically solid and spherical. Neither chromophil ridges nor budding in the fresh stool has been seen by us in what we regard as *E. coli* or in *E. dysenteriae*. This process must, of course, occur in those species also, in some form, whenever and wherever the contents of the cyst escape, but this has not been seen by us in stools, either fresh or old, or in stained preparations.

The relation of *C. dissimilis* to the so-called large race of *E. dysenteriae* is at present problematic. It has thus far probably been included in it. In our own material it by no means constitutes the whole of it, though it does form a considerable sector of it, not less than 25 per cent. Our extensive records and collection of slides had not been reviewed on this point at the time this paper was written. It is of sufficient frequency to enter into the problems of microscopic determination of specific infections, clinical observation, symptomology and therapy of human amebiasis.

SUMMARY

Nuclear structure in matured cysts of human intestinal amebas in fecal smears stained in iron hematoxylin afford a critical, easily available and satisfactory basis of specific determination of the different species occurring in man.

The nuclear structure is also available as one basis for generic distinctions. *Endamoeba* has predominantly nuclei with a solid spherical karyosome. *Councilmania* has predominantly nuclei with a more or less dispersed karyosome in the nuclei of easily matured cysts. Mitotic and metabolic phenomena modify the nuclear picture in the motile phase and in early phases of the encysted stage.

There are two amebas in human stools that have masqueraded under the cover of other species because of resemblances to them. *Councilmania tenuis* (described by Kuenen and Swellengrebel, 1917, as *Entamoeba tenuis*) belongs to *Councilmania* because of its dispersed karyosome. It has rather small 7.1 (from 3.1 by 5.7 to 8 by 10.6) microns, somewhat asymmetrically rounded cysts, with one, two, four, and eight nuclei, diffuse glycogen vacuole, few rounded to short rod-shaped chromatoidals, nuclear membranes often deformed, with little or no periph-

eral chromatin. Cysts are found budding freely in fresh stools. Both cytoplasm and nuclei stain faintly. There are motile stages with clear pseudopodia. The percentage in 2,587 persons is 9.2 per cent.

The second ameba, *Councilmania dissimilis*, has been confused with the large race of *Endamoeba dysenteriae*. It has clear pseudopodia in life. The glycogen vacuole is usually single at first, very large, eccentric and may show a stainable network, but later breaks up into smaller vacuoles. The chromatoidals are large, often asymmetrically angled, but sometimes squarish. Fifty cysts average 13 microns in diameter and range from 11.6 to 16.6 microns. Some are ellipsoidal. The percentage of infection in 2,587 persons was 0.4 per cent. The cysts are nearly spherical, have one, two, four, and eight nuclei, with peripheral chromatin massed in one large crescentic lateral blob on the membrane, karyosome in mature cysts, typically dispersed or made up of large granules.

I am indebted to Miss Inez Smith, M.A., examiner in my laboratory, for the first detection of the distinctive characteristics of *Councilmania dissimilis;* to Olive Swezy, Ph.D., and to Mrs. Dora Henry, M.A., for drawings of this species, to Miss Alfreda Kirsch, M.A., for drawing of *C. tenuis;* and to the Board of Research of the University of California, to Miss Ellen B. Scripps, and to other friends of the University for grants in aid of this research.

CULTURE METHODS, ENCYSTMENT AND EXCYSTMENT OF COUNCILMANIA DISSIMILIS KOFOID, IN CULTURE

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Since Sept. 25, 1925, for a period of twenty months, *Councilmania dissimilis* has been grown in Professor Kofoid's laboratory in mixed cultures with bacteria in various kinds of mediums mentioned. It grows abundantly in carefully made mediums at a constant temperature of 37.5 C.; however, the abundance varies with the different strains and even with the same strain. This would be expected, since the bacterial flora is never the same for any two strains, and in the cultures of the same strain there is variation of growth of the bacteria because the different kinds of organisms present vary as to the time of their separate lag periods; these, in turn, affect the lag period of the ameba.

From the stools of six patients, ten separate strains of *Councilmania dissimilis* Kofoid have been obtained in cultures in the Protozoological Laboratory of the University of California.

COMPARATIVE MORPHOLOGY

Councilmania dissimilis continues to reveal its morphologic characteristics even after long cultivation in artificial mediums; however, the large peripheral blob on the nuclear membrane of the resting nucleus, even though present, is not always as noticeable, since in culture amebas the stain decolorizes more easily than in nuclei of specimens in stools. The resting nucleus, as seen in figure 1, *A*, *B*, *C*, and *D* shows a linin network, like a spider's web, radiating out from the granular, dispersed karyosome. This network contains tiny chromatin granules, one at each junction of the fibers. In addition to the large curved peripheral blob, there are often smaller blobs distributed on the nuclear membrane.

Many division stages are visible on culture slides, and eight chromosomes have been counted on a number of spindles in dividing amebas in cultures as shown in figure 1, *D* of a nucleus in the anaphase with eight pairs of chromosomes. This fact definitely distinguishes *C. dissimilis* from *E. dysenteriae*, which has only six chromosomes (Kofoid and Swezy,[1] 1925).

Although the pseudopods appear clear and distinct from the granular endoplasm in living amebas, when stained they show an alveolar struc-

1. Kofoid, A., and Swezy, Olive: On the Number of Chromosomes and the Type of Mitosis in Endamoeba dysenteriae, 1925.

ture similar to that of the main body of the ameba, but they stain lighter and show distinctly the boundary between endoplasm and ectoplasm (fig. 1, *A*).

Figure 1, *E* and *F* represent cysts of the same strain produced in culture a year and a half old. The large nucleus shown in figure 1, *E* is not far removed from the precystic stage. It reveals the same characteristics as the resting nucleus of the motile forms. The nuclei of the cysts are similar to those in the original description given by Kofoid, except in the smaller amount of chromatin of the blob and karyosome.

These amebas in culture vary in size from 11.5 to 14 microns in diameter in the encysted stage.

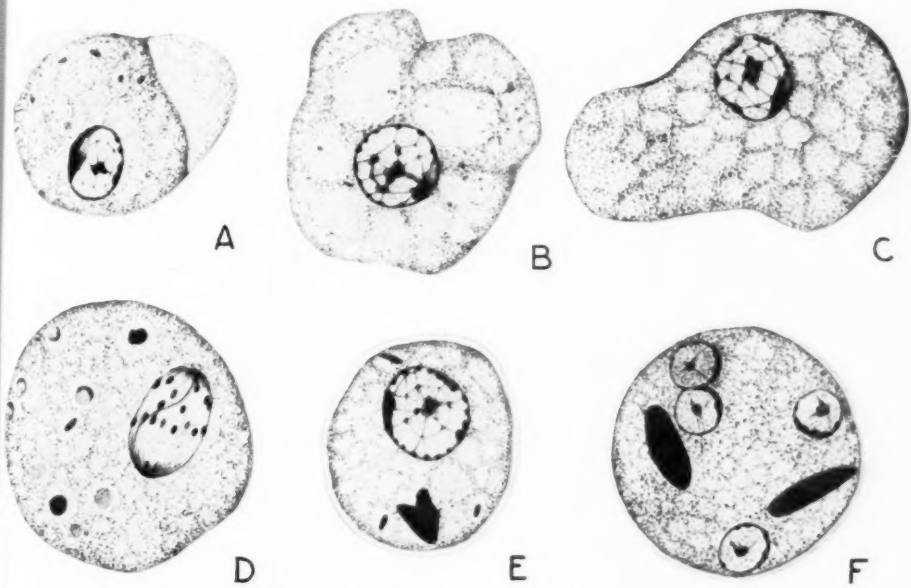

Fig. 1.—Councilmania dissimilis Kofoid from cultures in vitro. Reduced from a magnification × 3250.

A, motile form with broadly rounded pseudopods.

B and *C*, motile forms with resting nuclei. Note the dispersed karyosome, large curved peripheral blob in addition to smaller chromatin blobs on the nuclear membrane, also a network of linin fibers radiating from the karyosome.

D, motile form in mitosis with sixteen (eight pairs) of chromosomes at early anaphase. Note also the ingested bacteria. The delicate sigmoid line joining the polar centrosome is the intradesmose.

E, a precystic phase or early mononucleated cyst with large resting nucleus with lateral blob and the two small chromatoidals. A few bacteria still remain undigested even though the wall of the cyst has formed.

F, a four-nucleated cyst with two asymmetrically pointed chromatoidals.

MEDIUMS

The following mediums have been used to good advantage: Locke's-egg-albumin, Locke's-egg-serum, Locke's-serum, Locke's-egg-blood and Vogel's [2] starch-agar slants with buffered Ringer's or Locke's solutions added to them. The Locke's solution used is the modified formula given by Kofoid and Wagener; [3] they also added 0.5 per cent defibrinated blood to the Locke's solution used in covering the egg slants. For the Locke's-egg-blood medium, rat and rabbit blood have proved satisfactory, but rabbit blood is preferable, since it is more easily obtained in large quantities. Human, beef and rabbit serums have been tried. In the serum mediums used, the amebas are granular and extremely variable in size. Human serum gave better results than any of the other serums.

Drbohlav's formula,[4] Ringer's solution plus 1 per cent dextrin, is valuable for eliminating *Blastocystis hominis* and some flagellates such as *Chilomastix davainei* and *Enteromonas hominis;* it also helps in eradicating some undesirable amebas.

COMPARATIVE EXPERIMENTS OF COUNCILMANIA DISSIMILIS AND ENDAMOEBA DYSENTERIAE IN VARIOUS MEDIUMS

Cultures of *Councilmania dissimilis* and *Endamoeba dysenteriae* in the various mediums already mentioned, have been compared from time to time, during a period of fifteen months. In spite of many variables in these cultures, mixed with bacteria, some striking differences have been noted in three different strains of each kind of these amebas, all strains of each species giving the same characteristics for each experiment.

Councilmania dissimilis grows well indefinitely in Locke's-egg-albumin, while *Endamoeba dysenteriae* flares up, increasing considerably in numbers for the first twenty-four hours of the first transplant; it then continually decreases and many amebas die, until at the end of forty-eight hours there are fewer amebas than were originally put into each tube. This leaves a smaller number of amebas for the second transplant. This reduction continues from transplant to transplant until the amebas die out entirely by the end of two or three weeks in the forty-eight hour interval.

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2. Vogel, H.: Ueber Kulturen der Ruhramöbe und deren Beeinflussung durch Yatren, Arch. f. Schiff-u. Tropen-Hyg. **31**:74, 1927.

3. Kofoid, C. A., and Wagener, Edna Hannibal: The Behavior of Endamoebae Dysenteriae in Mixed Cultures with Bacteria, Univ. Calif. Pub. Zool. **28**:127, 1925.

4. Drbohlav, J.: Culture d'Entamaeba coli, Ann. de Parasitologie **3**:364, 1925.

Councilmania dissimilis also grows much better in Locke's-egg-serum than *Endamoeba dysenteriae*. *C. dissimilis* persists for a much longer time in this medium than *E. dysenteriae*, which fails to reproduce after the first flare-up and gradually dies out. Of the many tubes cultured, nine of *C. dissimilis* to one of *E. dysenteriae* reproduce well in twenty-four hours. For the first forty-eight hours, however, there are twice as many positive cultures of *E. dysenteriae* as in twenty-four hours; so the ratio at the end of forty-eight hours is on the average of nine tubes of *C. dissimilis* to two tubes of *E. dysenteriae*. After a few transplants, only *C. dissimilis* survives. Human serum was used for these experiments, and approximately the same number of amebas were put into each tube for each experiment.

ENCYSTMENT

Since twenty-four hour cultures contain more amebas than those forty-eight hours old, it was believed that by transplanting every day for a time, it would be possible to obtain the entire life cycle of *Councilmania dissimilis*. It was thought best to use Locke's-egg-blood medium, to have fresh rabbit blood on alternate days and to transplant every day for three days, observations of results to begin on the fourth day after making another transplant. Since the blood medium produces conditions approximating more nearly those existing in the human body, it was chosen in preference to that containing egg albumin. Observations on the amebas were made on cultures from one to forty-eight hours old, both from permanent slides and from mounts in iodine eosin.

This experiment has been performed four different times. Twice strains of *Endamoeba dysenteriae* were used by way of comparison in addition to cultures of *Councilmania dissimilis*. For these experiments, five different strains of *Councilmania dissimilis* and three different strains of *Endamoeba dysenteriae* have been used.

In every experiment, encystment resulted in cultures of *Councilmania dissimilis*. Cysts of *Endamoeba dysenteriae* were not found in any tubes.

EXCYSTMENT

The stool material from which nine of the stains were cultured contained many cysts and few motile forms, two of them did not appear to have any motile forms. In each case, prolonged search did not reveal cysts in the cultures by the end of forty-eight hours after the original inoculation, but numerous active amebas were present.

Culture cysts produced in the foregoing experiments also excysted if allowed to remain in the incubator without being disturbed for about forty-eight hours after formation. Budding cysts have been found in original material and in cultures from time to time.

SUMMARY

1. Ten strains of *Councilmania dissimilis* have been cultured in various mediums, principally in Locke's-egg-blood and Locke's-egg-albumin. It also grows in serum without slants according to Craig's [5] method. This ameba has been cultured for the past twenty months in this laboratory. Cultures of *C. dissimilis* compared with those of *E. dysenteriae* show that both amebas grow equally well in Locke's-egg-blood; whereas in Locke's-egg-albumin, *C. dissimilis* grows indefinitely but *E. dysenteriae* dies out after a few transplants. The ratio of survival of *C. dissimilis* and *E. dysenteriae* in Locke's-egg-serum is nine tubes of the former to two of the latter for the first forty-eight hours. *C. dissimilis* will also persist for a long time in Locke's-egg-serum, and *E. dysenteriae* lives in it for only a few transfers.

2. Encystment of *Councilmania dissimilis* has been produced in cultures by daily transplanting into Locke's-egg-blood, using only fresh blood. These same methods have failed to produce cysts of *Endamoeba dysenteriae* in our cultures.

3. Excystment of *C. dissimilis* has been produced from specimens of stools in culture and from cysts that were experimentally developed in cultures.

4. *Councilmania dissimilis* in culture has eight chromosomes, a large curved peripheral blob and a dispersed karyosome, which are not characteristics of *E. dysenteriae*.

5. Craig, C. F.: A Simplified Method for the Cultivation of Endamoebae Histolytica, Am. J. Trop. Med. **6**:333, 1926.

PRESENTATION OF CASE OF INFECTION WITH COUNCILMANIA DISSIMILIS KOFOID

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The following case represents one of the few relatively simple infections with *Blastocystis, Giardia enterica,* the three species of *Councilmania* and *Endolimax nana.* It offers the advantage of not having an admixture of *Endamoeba dysenteriae* or *Endamoeba coli* infections. Therapeutically, it is interesting because of the susceptibility of *Giardia enterica, Councilmania lafleuri* and *Councilmania tenuis* to full doses of antimony trioxide and the resistance of *Councilmania dissimilis* to this medication. It is also interesting to see both *Councilmania dissimilis* and *Endolimax nana* disappear after doses of stovarsol. It is to be borne in mind that we feel it is too early to judge of the thoroughness of the eradication, and that rechecking of the physical and laboratory observations is necessary for a period of two years before a presumptive "cure" can be granted. At present, the return of a large mononuclear count of 8 per cent suggests that the eradication is possibly not so complete as the examinations of the stool would lead one to believe.

REPORT OF CASE

A man, aged 38, white, married, who presented himself in July, 1926, said that a definite pain in the upper portion of the left side of the abdomen came on after attending a picnic in May, 1924. The pain continued, but remission occurred for periods as long as six, eight or ten months. There had not been complete relief since December, 1925. Birth had been normal; the patient had heard that his mother was lacerated at confinement. He had been breast fed for the first nine months of infancy. During childhood he had had whooping cough, measles, chickenpox and scarlet fever, but he had not had especially severe attacks. At 17, he had three severe attacks of appendicitis, the last ending in operation with drainage. Drainage caused a hernia, which was successfully repaired. His tonsils were "clipped" and later enucleated. A deviated nasal septum was repaired in 1911. He had had a light attack of influenza in 1918. He did not say that he had had venereal disease.

Residence for a period long enough for the eating of a meal had included France, Italy, Switzerland, Germany, England, Canada and practically all of the states of the United States. The father died at the age of 62 of cancer—"beginning in the neck." The patient could not be more specific. The mother, aged 63, on whom hysterectomy had been performed, was alive and well. One brother was alive and well.

Two sisters were alive—the elder was well; the younger had pulmonary tuberculosis and had recently had a collapsing operation of the chest.

The patient's wife, slightly younger, was alive and well after treatment for *Councilmania* infection. Two small sons, aged 3 years and 6 years, were alive and well. The elder son had had moderate adenopathy of the neck.

The patient's status was as follows: The appetite was excellent—the patient said "too good." The digestion was normal, that is, food did not cause distress. The bowel habit had been one evacuation about every thirty-six hours. Recently, it had changed to one evacuation every twenty-four hours. There was seldom nycturia. The patient slept soundly, not less than eight hours—and rose refreshed. He estimated his muscular strength at normal. His weight had not changed much in a year, but he thought that it might be increasing slightly. He was not especially nervous, although he had been depressed occasionally during the past year. He considered his sexual powers normal, or but slightly below normal.

Examination.—The physical examination revealed a well nourished man, aged 38, with a temperature of 98 F. The pulse rate was 84; the respiratory rate was 16 plus, and the blood pressure was 174 systolic and 104 diastolic. These rates were normal and were taken while the patient was in a supine posture. He was 68½ inches (173.9 cm.) in height and weighed 146 pounds (66.2 Kg.), his previous maximum weight being 152 pounds (68.9 Kg.). The hair, skin and vertebral column were normal. The eyes were normal, and glasses were worn only occasionally. The conjunctivae were slightly and chronically injected. A few small meibomian cysts were present. The muscular movements and light and accommodation reflexes were normal.

The drum of the left ear was definitely sclerosed; the drum of the right ear was normal. The hearing was as follows: Right: $\frac{\text{normal}}{\text{normal}}$; left: $\frac{0}{0}$.

The airways of the nose were narrow. There was a slight chronic rhinitis. The teeth were well preserved and well kept. There were a few small gold fillings. The tonsils had been removed. The pharynx showed a chronic inflammation with dilated vessels and a mild "blobbing" of the mucosa. The neck was normal. The shape of the chest was symmetrical. The anteroposterior diameter was less than normal, resulting in a flattening.

The mammae and nipples were normal. The lungs did not show signs of activity of any pulmonary lesion. Observations from inspection, palpation, percussion and auscultation were normal. The point of maximum impulse of the heart was within normal limits in the fifth interspace. The area of cardiac dulness was of normal size. The heart sounds were normal.

Examination of the abdomen revealed an old appendectomy scar with evidence of repair. The liver was from 17.5 to 19.5 cm. in diameter in the right midclavicular line. The edge of the liver was palpable from two to three fingerbreadths below the costal margin. The spleen was not palpable. The cecum was slightly sensitive on palpation. The area of the sigmoid colon was sensitive on palpation. The left flank was also sensitive to pressure on palpation. The inguinal areas were normal. The genito-urinary system showed normal conditions.

The nail of the great toe on the right foot was nodular. There was a small scar over the left patella. The patellar reflexes were equal and normal, and the anterior and longitudinal arches were normal.

On entrance to our service, examination of a single specimen of urine taken in the afternoon showed that it was amber and clear with a specific gravity of 1.022. The reaction was acid. There was a faint trace of albumin with the heat and acetic acid test. Benedict's test did not reveal dextrose; indican was not found.

Microscopic Examination.—Examination of a centrifugalized specimen revealed: occasional leukocytes, one hyaline cast, no cystals; an occasional squamous and spherical epithelium, and no red blood cells or bacteria.

A recheck of the urine one month later did not show any albumin.

A recheck of the urine eleven months later showed: a light amber, clear specimen, 2,440 cc. in twenty-four hours, with a specific gravity of 1.012. The reaction was slightly acid. No precipitate of albumin occurred with heat and acetic acid test. Neither dextrose nor indican were found. There was 29.2 Gm. of urea.

Microscopic examination of a centrifugalized specimen revealed an occasional leukocyte, no casts or crystals; an occasional squamous, and spherical epithelium; no red blood cells or bacteria.

The serological observations during blood Wassermann test were as follows: cholesterinized beef heart antigen, (— — —); acetone-insoluble antigen, (— — —), and alcoholic extract antigen, (— — —).

Examination of the blood on entrance to the hospital revealed erythrocytes, 5,075, per cubic millimeter; morphology, normal; immature and degenerate types, none; hemoglobin (Dare method), 90 per cent; color index, 0.9, and leukocytes, 9,400 per cubic millimeter.

The differential count revealed: neutrophils, 56.3 per cent; large mononuclears and transitionals (combined count), 8 per cent; lymphocytes, 35.3 per cent; eosinophils, none; basophils, 0.33 per cent; immature and degenerate types, none, and blood parasites, none.

A recheck of the complete blood count three months later showed: erythrocytes, 5,000,000 per cubic millimeter; morphology, normal; immature and degenerate forms, none; hemoglobin (Dare method), 88 per cent; color index, 0.8; leukocytes, 8,800 per cubic millimeter; neutrophils, 50 per cent; large mononuclears, 5 per cent; lymphocytes, 44.3 per cent; eosinophils, 0.33 per cent; basophils, 0.33 per cent; immature and degenerate types, none, and parasites, none.

A recheck of the complete blood count eleven months later showed: erythrocytes, 5,010,000 per cubic millimeter; morphology, normal; no anisocytosis; immature and degenerate forms, none; hemoglobin (Dare method), 90 per cent; color index, 0.9 and leukocytes, 8,800 per cubic millimeter.

The differential count revealed: neutrophils, 51.3 per cent; large mononuclears, 8 per cent; lymphocytes, 4 per cent; eosinophils, 0.33 per cent; basophils, 0.33 per cent; immature and degenerate types, none and parasites, none.

Bacteriologic studies of the feces two months after entrance to the hospital showed consistently in three different examinations only lactose fermenters. Six months after entrance, culture gave acid in lactose. A week later, a gram-negative, nonlactose fermenter was picked up with the following reactions and description: gram-negative rod; nonlactose fermenter; arabinose, plus; maltose, plus; mannite, plus; xylose, plus; dextrose, plus; sucrose, plus; salicin, plus; milk coagulated; hydrogen sulphide, plus; nitrates reduced and indol. An autogenous vaccine was prepared from this organism.

Sigmoidoscopic Examinations.—Examinations were made on the following dates with the recorded results indicated:

July 24, 1926: Dilated vessels: moderate "blobbing"—meaning by this term a heaping-up process, a coarse granulation, such as one sees in the post-pharyngeal wall in the presence of a chronic inflammation; mucus (free). A diagnosis of chronic colitis was made.

July 26: Hyperemia; dilated vessels both fine and moderate in size; a moderate scattered "blobbing." A diagnosis of chronic colitis was made.

September 16: Hyperemia; dilated vessels; definite scattered "blobbing." A chronic colitis was diagnosed with little evidence of recession.

April 19, 1927: Dilated vessels; coarse "blobbing." A diagnosis of chronic colitis was made. The principal evidence of recession lies in a diminished hyperemia.

Examinations of the Stool.—Examinations of the stool in this case were made by Professor Kofoid and Miss Virginia Hall at six different intervals, with a total of twenty-nine stools shown in table 2.

TECHNIC OF SIGMOIDOSCOPY

The instrument, a specially built Cameron sigmoidoscope, with an excellent telescopic attachment, is lubricated well and gently inserted, pointing at first at the patient's umbilicus. The only preparation is evacuation. The results are read ahead of the distal end of the instrument, and inflation occurs only spontaneously at atmospheric pressure. With care and the exercise of patience, the instrument can be inserted easily in many cases as high as 14 to 17 inches (35.4 to 42.55 cm.) from the anal splimeter. In some spastic cases, a single dose

TABLE 2.—*Examination of the Stool*

Date	Number of Stools Examined	Organisms, Number of Stools Infected					
		Blasto-cystis	Giardia enterica	Councilmania lafleuri	C. tenuis	C. dis-similis	Endolimax nana
July 7-10, 1926	5	4	1	2	1	2	2
July 23-29	6	6	0	1	2	3	5
August 4-9	6	1	0	0	0	1	1
August 21	1	0	0	0	0	0	1
February 15-21	6	4	0	0	0	4	2
April 25-28	5	1	0	0	0	0	0

of morphine sulphate (one-eighth grain [0.008 Gm.] to one-sixth grain [0.010 Gm.] with atropine sulphate one two hundredth grain [0.0003 Gm.] hypodermically injected) or a day's medication with benzyl benzoate (20 drops in water every four hours for twenty-four hours) is needed as preparation.

Occasionally some grade of prolapse of the rectal mucosa or even a mild redundancy makes insertion more difficult.

The use of the customary inversion table, breathing by the patient as directed, inflation in rare cases, help one in these more difficult cases.

A few of the English writers have somewhat doubted the necessity of the inversion table—in our experience it is invaluable, and its use is the first step in converting sigmoidoscopy from an uncertain and obscure and coarse procedure into one to which the most sensitive patient can be subjected with precision.

Examination for intestinal parasites showed only the occurrence of *Councilmania dissimilis.*

TREATMENT

The first treatment undertaken was with antimony trioxide, chemically pure, given in gelatin capsules in a dose of 2½ grains (0.162 Gm.) three times a day after meals, the first week—then increased to two capsules three times a day after meals, till the total quantity of 300 capsules were taken.

In using antimony trioxide, we have found it necessary to test all material for the presence of arsenic. A number of batches of the drug have been discarded because of the presence of minute traces of arsenic.

Because of the chronic colitis present, installations of iodoxy quinoline sulphonic acid (1.75 Gm. in 250 milliters of water at 105 F.) were begun and given every forty-eight hours till sixty-five doses had been given.

Two months after entrance, sodium cacodylate in 13 per cent solution in 1 milliliter doses was given hypodermically two to three times a week.

A recheck of the feces four months after the patient's entrance to the hospital showed again the presence either anew or continued of *Coucilmania dissimilis*.

As *Councilmania lafleuri*, in our experience, has been readily susceptible to antimony trioxide, we decided with this *Councilmania dissimilis* to use cetarsone stovarsol (3 aceytlamine, 4 hydroxy-phenylarsonic acid) in the original tablet, in dose of 0.25 Gm., the total number being 30. One tablet was given twice a day during the first day, then one tablet three times a day after meals, with water freely, till all were taken. Contrary to possible expectation, there was no reaction to this form of arsenic.

Occasionally we have used these tablets crushed and put up in enteric coated capsules—i.e., coated with phenyl salicylate. It was more with the idea of minimizing the irritation caused by the gastric mucosa that the enteric phenyl salicylate coat was used, since they do not act in an acid medium, but rather in an alkaline one. Raiziss[1] of the Dermatological Research Laboratory of Philadelphia is responsible for this statement.

It is curious that while this patient showed a trace of albumin in his urine on entrance, there was no evidence of irritation following the use of the acetarsone. Many other patients, however, have shown definite evidence of irritation after moderate use of it.

The reactions in one instance in a man weighing between 150 and 165 pounds (68 Kg. to 74.8 Kg.) were of the nitritoid variety and occurred after the ingestion of one-half tablet or 0.125 Gm. of acetarsone. The rest of the unfavorable reactions were of the type incidental to poisoning with arsenic. A macular rash of skin and mucous membrane, fever, intense aching and desquamation occurred.

A woman suffering from arthritis deformans and of about 150 pounds weight, had intense desquamation from head to foot after a

1. Raiziss and Gayron: Organic Arsenical Compounds, New York, The Chemical Catalog Company, Inc., p. 360; J. Am. Chem. Soc. **43**:583, 1921. Farb. M. L., and B. U. S. P. 1077, 462. Christiansen: J. Am. Chem. Soc. **44**: 2340, 1922.

dosage of 0.25 Gm. (1 tablet) daily for five days. This patient's enlarged liver and inability to gain weight on fats was suggestive of hepatic incompetency. This suggestion became more certain when the arsenic did not cause so brisk a reaction.

COMMENT

A discussion of this case of *Councilmania dissimilis* infection should emphasize a few simple points.

In the first place, contrary to the majority of infections with *Endamoeba dysenteriae* of such long standing, the enlargement of the liver is not pronounced. In the presence of *Endamoeba dysenteriae* infections of this standing it is common to find livers with a midclavicular diameter of the right lobe of from 21 to 27 cm., and a projection of the edge of the liver below the costal margin of from three to five finger-breadths.

The other notable observation has been in the percentage of large mononuclears in the blood count. We found 8 per cent, early, and after some treatment, 5 per cent. Our last percentage, taken recently, was again 8 per cent. A relative increase in the percentage of large mononuclears is common and seems to be present rather consistently in both *Endamoeba dysenteriae* and the various *Councilmania* infections. The occurrence of a chronic colitis is characteristic of both *Councilmania* and dysentery amebic infections. It is difficult to differentiate between the two clinically, and one usually has to avail himself of the history and the behavior of the liver as checks in order to form an opinion as to whether the case is clinically one of *Councilmania* infection or one of infection with *Endamoeba dysenteriae*.

In regard to the bacterial commensals, we have found it of advantage to classify them first as to whether or not they are lactose fermenters, and then also to decide whether they fall within the putrefactive or the saccharolytic group. For the time being, that is within the last nine months, since October, 1926, we have been making autogenous vaccines from the nonlactose fermenters. Occasionally, however, we have made autogenous vaccines from the lactose fermenters for treatment in these cases of chronic colitis.

Nine months' experience with this type of vaccine therapy as an adjunct in the care of these patients has hardly justified an opinion, but it can be stated that we have seen in this length of time a sufficient number of patients benefited by the vaccine therapy to warrant our continuing the labor and expense of our work.

It is not uncommon to find a patient improving after the eradication of his protozoan infection and finding some degree of his symptom complex continuing. In addition, the patient in this case has continued to improve on vaccine therapy until complete recovery has occurred.

In regard to the use of iodoxy quinoline sulphonic acid, it is interesting to note that we have had four years of experience with it in Berkeley, and that we have not seen any case that convinced us of its ability to eradicate well established infections with either of the three species of *Councilmania* or with *Endamoeba dysenteriae*.

I have found it an excellent adjunct, however, in the treatment of patients with chronic colitis, which is so prevalent, and have found it much more efficacious than quinine solution, the various oils and other remedies.

It is, however, by no means innocuous in its properties. We have seen a number of persons show definite and intense irritation of the bowel as a result of its use. We have also seen a series showing thyroid hyperactivity from the use of iodoxy quinoline sulphonic acid.

We feel from our own experience that it is not a drug to be trusted without adequate observation of the patients. It is an efficacious adjunct in the treatment of patients with amebic infection and the accompanying chronic colitis, but is not a first-class eradicator.

SUMMARY

This case of infection with *Giardia* and the three species of *Councilmania* is interesting, first, because it presents a definite symptomatology. The host to these parasites is ill. There is genuine subjective and objective evidence of it. The clinical behavior is somewhat like that in cases of chronic amebiasis in the temperate zone due to infection with *Endamoeba dysenteriae*. However, it is different qualitatively. There is, apparently, less invasion of the upper digestive tract. There is not a measurable increase in the size of the liver.

The therapeutic behavior has been discussed in the opening paragraphs.

From the patient's point of view, his gain has been in the disappearance of discomfort, increase in muscular and nervous vigor, absence of mental depressions and increased ability to meet the strain of his work. He sums it up by saying that he has not felt so well in at least three years.

From the clinical point of view, the gain has been the receding of a chronic inflammatory condition of the colon.

VARIATIONS IN THE REDUCING POWER (SUGAR) OF NORMAL HUMAN BLOOD*

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Although the literature contains numerous determinations of the blood sugar in man, it seems to us that for some reason most of this material is unsatisfactory for the purpose of establishing a norm or reference level. We agree with Gray [1] (1923) that: "Standards should be founded not only on a careful examination of a few persons, but on a statistical analysis of many persons." His search of the literature yielded only two series of blood sugar determinations which he considered long enough for statistical treatment, and we find that only few satisfactory series have appeared since his paper was written.

Many of the longer series which have been published are based on hospital material, and although we may be told that the patients were under treatment for conditions which were presumed not to have any effect on the blood sugar, the fact that they were under treatment at all is, in our estimation, sufficient to exclude them from consideration as normal subjects. Determinations made on convalescents are open to the objection that one cannot properly evaluate the effects of prolonged and enforced rest (Riddle and Honeywell,[2] 1923-1924), a modified or perhaps restricted diet and the medical or surgical treatment previously undergone. Moreover, it would be extremely difficult to duplicate such a series should one desire to test the basis of any conclusions which the authors may have drawn.

Those series which are based on normal men are usually short, and while the subjects may be considered as normal in the sense that they do not have any apparent disease, they often differ widely in age, activity and habits of living. Frequently the subjects and their preparation for the test are not described. In none of the work which has come to our attention is there any attempt to show that the results are truly representative of the general field from which the observations were drawn.

In the present research, attention was directed to the following points:

(1) The establishment with a fair degree of precision of a blood sugar norm, or reference level, which presumably could be duplicated in other laboratories.

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* From the Department of Physiology, Columbia University.

1. Gray, H.: Blood Sugar Standards in Conditions Neither Normal Nor Diabetic, Arch. Int. Med. **31**:241 (Feb.) 1923.

2. Riddle, O., and Honeywell, H. E.: Am. J. Physiol. **57**:333, 1923.

(2) Determination of the minimum number of observations necessary to establish a significant series, i.e., a series which would be representative of this general field, within predictable limits.

(3) Investigation of the constancy of the blood sugar level in a group of normal persons, a point which has often been stressed in the literature. We wished to test this constancy on uniform material under carefully standardized conditions.

(4) Determination of the optimum type of series which would most truly represent the field, e.g., whether for this purpose it is more desirable to make twenty-five observations on one subject or one observation on each of twenty-five subjects.

Our subjects were normal, healthy young men and women, students in the medical school, who volunteered for the work, and who were thoroughly familiar with the requirements of the research and the technic involved so far as it concerned them. They came to the laboratory without breakfast and rested comfortably on cots for from twenty to thirty minutes before the taking of the blood sample. At the end of the rest period, a superficial vein in the bend of the elbow was selected and a tourniquet applied to the upper arm; immediately about 2.5 cc. of blood was drawn into a syringe containing a small amount of dry sodium oxalate. With this technic, clotting did not occur. In this connection, it may be observed that a clean, sharp needle of relatively small size (24 gage) makes for quickness and ease in obtaining the sample with a minimum of discomfort to the subject. None of the subjects gave any indication of apprehension, fear or marked discomfort at any time during the period. All the samples were secured between 9 and 10 a. m.

Blood sugar determinations were made in duplicate, the Shaffer-Hartmann [3] method (1920-1921) and the conversion table of Duggan and Scott [4] (1926) being used. All the determinations were made by the same analyst, who was thoroughly familiar with the technic, and variations in the technical results were insignificant in comparison with the physiologic variations.

Our first series consisted of 141 observations, each made on a different person. The mean age of the subjects was 23 years, with a mean deviation of $\pm$ 3.4 years; the mean weight (132 subjects only) was 68.5 Kg., with a mean deviation of $\pm$ 10.3 Kg. When occasion required that more than one sample be taken from a person, only the initial sample was included in this series, so that the results are comparable in this respect. The raw data are presented in table 1 in the order in which the observations were made.

3. Shaffer, P. A., and Hartmann, A. F.: J. Biol. Chem. **45**:365, 1920.

4. Duggan, W. F., and Scott, E. L.: J. Biol. Chem. **67**:287, 1926.

To show that this series actually represents the general field within the limits of precision which we claim, and to determine whether a shorter series would have accomplished the same purpose with a satisfactory degree of precision, these data were submitted to the analytic treatment described by one of us (Scott,[5] 1927). The series of 141 observations was divided into component series of 5, 10, 20, 28, 35 and 47 observations each. The means (M), mean deviations (ϵ) and the mean deviations of the means (ϵ_M) of these series were then computed, and are presented in their natural order in table 2. The characteristic ϵ_M for each group of series of a given number of observations was then determined by two different methods. In the first method, it was presumed that ϵ for the series of 141 did not differ from ϵ for a series of

TABLE 1.—*Raw Data of 141 Blood Sugar Observations made on 141 Medical Students* *

94	94	99	104	96	93	96
84	102	102	97	115	96	91
84	102	105	105	116	98	100
92	94	93	97	102	105	96
102	94	93	101	97	91	96
102	94	99	95	98	96	96
84	102	115	99	104	89	88
108	92	116	98	96	93	91
110	94	88	96	92	101	94
110	99	110	91	102	92	98
102	89	99	94	89	89	89
94	99	106	94	87	96	92
88	97	93	92	97	91	92
84	107	105	93	94	93	91
96	102	96	82	102	88	93
102	102	101	96	97	97	94
110	102	102	94	96	109	92
82	105	98	106	92	98	91
97	99	98	82	89	91	89
102	98	94	89	102	83	99
						87
Mean						97
Mean deviation						7.0

* The observations are presented in the order in which they were made.

an infinite number of observations by an amount which was physiologically significant. Therefore ϵ for the 141 observations was divided by the square root of the number of observations which was characteristic for the series of each of the groups. The quotients were considered as the "true" ϵ_M's for series of the respective lengths (table 3, column 4). In the second method, the ϵ_M's for each group were derived empirically, by considering each M of the group as an original observation and determining ϵ for these means by the formula:

$$\epsilon = \sqrt{\frac{\Sigma d^2}{N-1}}$$

The results are presented in table 3, column 5. It will be seen that in every case the empirical ϵ_M is greater than the "true" ϵ_M by approximately

5. Scott, E. L.: J. Biol. Chem. **73**:81, 1927.

1.2. In making predictions, this fact must be taken into consideration. Safe predictions cannot be made with the precision indicated by a strict interpretation of the theory of probabilities, and to make safe prediction with a 95 per cent probability one should add 2.4 to twice the mean deviation of the mean or make other allowance for this discrepancy.

The mean deviations of the mean deviations (ϵ_ϵ) were calculated in a manner similar to that employed for the empirical ϵ_M's, except that the ϵ's of each group were now treated as the original observations. The value $\epsilon_{\epsilon'}$, measures the variation of ϵ in a manner similar to that in which the variability of M is measured by ϵ_M. Before a series can be considered

TABLE 2.—*The Means, Mean Deviations and the Mean Deviations of the Means of The Component Series of the Grand Series of 141 Blood Sugar Observations*

Group I 28 Series of 5 Each			Group II 14 Series of 10 Each			Group IV 5 Series of 28 Each		
M	ϵ	ϵ_M	M	ϵ	ϵ_M	M	ϵ	ϵ_M
91	7.6	3.3	97	10.8	3.4	96	8.4	1.6
102	9.5	4.2	96	8.9	2.8	100	6.8	1.3
92	7.1	3.2	96	4.1	1.3	97	7.6	1.4
98	10.4	4.6	100	5.0	1.6	95	4.9	0.9
97	4.3	1.9	102	9.5	3.0	94	4.9	0.9
96	4.2	1.9	99	4.4	1.4			
98	6.7	3.0	98	4.2	1.3			
101	2.8	1.3	92	6.9	2.2			
98	5.4	2.4	102	8.0	2.5	Group V 4 Series of 35 Each		
106	11.9	5.3	94	5.3	1.7	M	ϵ	ϵ_M
100	5.6	2.5	95	4.9	1.5	97	7.9	1.3
98	3.2	1.4	94	7.1	2.2	100	6.1	1.0
100	3.9	1.7	94	3.7	1.2	96	7.4	1.2
96	3.1	1.4	92	2.9	0.9	94	4.7	0.8
87	6.8	3.0						
93	8.6	3.8						
105	9.7	4.3	Group III 7 Series of 20 Each					
98	4.8	2.1						
94	6.0	2.7						
95	5.0	2.2	M	ϵ	ϵ_M	Group VI 3 Series of 47 Each		
96	5.5	2.4						
94	4.6	2.1	96	8.7	1.9	M	ϵ	ϵ_M
91	3.2	1.4	98	4.3	1.0			
96	9.6	4.3	100	7.4	1.7	98	7.6	1.1
96	3.2	1.4	95	6.4	1.4	98	7.6	1.1
93	4.0	1.8	98	7.6	1.7	94	5.0	0.7
91	1.6	0.7	94	5.7	1.3			
93	3.8	1.7	93	3.4	0.8			

satisfactory, it is necessary that the variability of both M and ϵ be rendered reasonably small, but it is even more important that the variability which remains be reduced to an approximately constant value. The values found for ϵ_ϵ are shown in table 3, column 7. It will be seen that ϵ_ϵ continually diminishes as the number of observations in the series increases, but at a decreasing rate until at about twenty-eight observations the rate of decrease becomes so low that for practical purposes ϵ_ϵ may at this time be considered a constant.

In table 3, column 6, are given the means of the ϵ's of the respective groups. These will be seen to increase, but also at a decreasing rate as the number of observations becomes greater, until they too become approximately constant at about twenty-eight observations. Thus at

about twenty-eight observations, the range of variation for the first time is covered characteristically (Scott, 1927). This indicates that twenty-eight is the minimum number of observations necessary to establish a significant series.

The growth of the series is illustrated in chart 1. Note the tendency of the mean to find its final level and of the hatched area—ϵ—to assume a constant width. When these two functions, with reasonable probability, have become sufficiently constant for the purposes of the research, there is no practical point in adding observations. Before this, safe prediction cannot be made.

When a large number of observations is available, it is possible to test the adequacy of a series by comparing the actual distribution of the observations with that predicted from the mean and the mean deviation of the series to be tested. Table 2 shows such great variations of both

TABLE 3.—*Analysis of the Variability of the Various Component Series, as Revealed by a Study of the Behavior of the Mean Deviations, Mean Deviations of the Means and the Mean Deviations of the Mean Deviations*

1 Number of Observations in the Series N	2 Number of Series in the Groups n	3 The Means of the Means $\frac{\Sigma M}{n}$	4 Theoretical Mean Deviation of the Means $\frac{7^*}{\sqrt{N}}$	5 Empirical Mean Deviation of the Means (See text)	6 The Mean of the Mean Deviations $\frac{\Sigma \epsilon}{n}$	7 Empirical Mean Deviation of the Mean Deviation (See text)
5	28	96	3.1	4.3	5.8	2.6
10	14	96	2.2	3.4	5.9	2.4
20	7	96	1.6	2.7	6.2	1.9
28	5	96	1.3	2.3	6.5	1.6
35	4	96	1.2	2.6	6.5	1.4
47	3	97	1.0	2.3	6.7	1.5

* ϵ for 141 observations.

M and ϵ for the series of five and ten observations that it is evident that these series do not permit any precise prediction.

The actual 141 observations are compared with the predicted observations on each of the component series which contained more than ten observations (table 4). The first row at the top of the table gives the distribution as predicted from the theory. The numbered rows which follow show the actual distribution of the observations about the mean of the indicated series. The last three rows of each group show, respectively, the mean distribution for the group, the mean deviation about this mean in absolute units and the mean deviation in percentage of the total number of observations. Though there are so few of the longer series in their respective groups that ϵ for their distribution is presumably not yet fixed, it would seem safe to assume on the basis of the table taken as a whole, that safe prediction can be made with a probability of about 95 per cent and to a precision of about 3ϵ when there are twenty-eight

or more observations in the series. It will be noted that when this test is applied to the series from our own laboratory (table 5), and to those of Okey and Robb,[6] all of the means fall within the predicted limits.

As a result of this analysis, we may conclude that approximately twenty-eight is the minimum number of observations which are necessary before the series may be said to represent the field fairly, and so is the minimum permissible in work with material of this type. It is also the optimum number, for fewer observations would not permit prediction, and it is doubtful whether more would increase the precision sufficiently to justify the added expense of time and effort.

Since twenty-eight constitutes a satisfactory series for the establishment of both M and ϵ, we have in the series of 141 observations a factor of safety of about 400 per cent. Hence it would probably be safe to infer that within the limits of known physiologic significance, the true

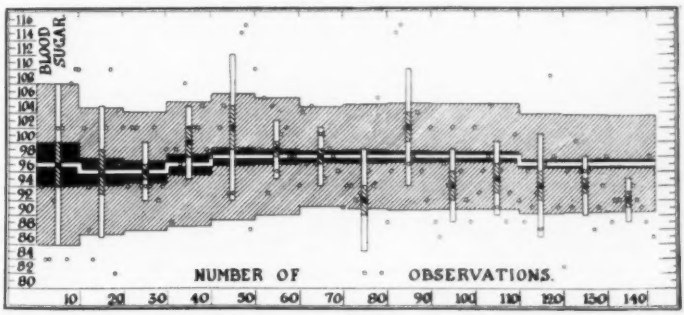

Chart 1.—Chart showing the growth and stabilization of the series of 141 blood sugar observations which were made on medical students. The individual determinations are shown in their natural order and are indicated by circles; the means (M) by dots; the mean deviations (ϵ) by outline bars, and the mean deviations of the means (ϵ_M) by hatched bars. The central field shows the characteristics of the cumulative series by increments of 10. The white line indicates the mean; the hatched area the mean deviation and the solid black, the mean deviation of the mean of the growing series.

mean and mean deviation have been established to a precision of three times the mean deviation found. From this it follows that the chances are ninety-five out of 100 that the mean of any series of blood sugar observations made on twenty-eight or more persons under the conditions we have described will not differ by more than three times its mean deviation from 97 mg. per hundred cubic centimeters, the mean of our series of 141 observations.

6. Okey, R., and Robb, E. I.: J. Biol. Chem. **45**:165, 1925.

TABLE 4.—*Fulfillment of Predictions Concerning the 141 Consecutive Observations Made from Each of the Component Series Which Included Twenty or More Observations*

	Frequency							
	± ε	± 2ε	± 3ε	± 4ε	N	M	ε	ϵ_M
	Predicted							
	96	135	140	141	141			
Group III, 20 Observations in Each Series								
1	120	137	141	141	141	96	8.7	1.9
2	74	108	129	134	141	98	4.3	1.0
3	85	131	141	141	141	101	7.4	1.7
4	120	137	141	141	141	96	8.7	1.9
5	108	133	141	141	141	98	7.6	1.7
6	91	130	137	141	141	94	5.7	1.3
7	54	93	118	131	141	93	3.4	0.8
Mean frequency	93	124	135	138				
ε (absolute)	25	16	9	4				
ε (percentage)	18	11	6	3				
Group IV, 28 Observations in Each Series								
1	113	137	141	141	141	96	8.4	1.6
2	92	129	141	141	141	100	6.8	1.3
3	114	137	141	141	141	97	7.6	1.5
4	79	120	137	139	141	95	4.9	0.9
5	86	119	133	137	141	94	4.9	0.9
Mean frequency	97	128	139	140				
ε (absolute)	16	9	7	4				
ε (percentage)	11	6	5	3				
Group V, 35 Observations in Each Series								
1	114	137	141	141	141	97	7.9	1.3
2	83	127	141	141	141	100	6.1	1.0
3	107	137	141	141	141	96	7.4	1.2
4	86	119	137	139	141	94	4.7	0.8
Mean frequency	92	130	140	140				
ε (absolute)	16	9	2	1				
ε (percentage)	11	6	1	1				
Group VI, 47 Observations in Each Series								
1	108	134	141	141	141	98	7.6	1.1
2	108	134	141	141	141	98	7.6	1.1
3	86	119	133	137	141	94	5.0	0.7
Mean frequency	100	129	138	140				
ε (absolute)	13	9	5	2				
ε (percentage)	9	6	4	1				

TABLE 5.—*Three Consecutive Observations from Each of Twenty-Five of the 141 Subjects Shown in Order in Columns 1, 2 and 3*

	Observation				Observation		
Subject	1	2	3	Subject	1	2	3
1	94	92	92	14	94	94	102
2	84	96	84	15	102	99	99
3	84	99	102	16	92	102	102
4	92	102	102	17	89	102	94
5	102	110	102	18	99	94	110
6	110	108	93	19	107	97	94
7	102	96	99	20	102	87	102
8	82	94	84	21	102	92	105
9	102	94	97	22	105	92	99
10	94	97	105	23	99	93	96
11	94	97	105	24	92	96	92
12	102	92	102	25	105	97	82
13	94	92	94				
Mean					97	97	97
Mean deviation					± 6.7	4.7	6.1

Chart 2 shows not only that the means of such series behave in the manner described, but also that when ϵ_M is calculated from a stabilized ϵ, the means of series as short as five or ten observations fall within these limits. The explanation of this is that the mean is established somewhat earlier than is the mean deviation, so that while it might be possible to predict limits for the true mean from such short series if we had a reliable measure of probability, we are actually unable to do so because the measure of deviation derived from such short series is untrustworthy. Again, with such short series the precision of the mean is so low (chart 2) that predictions made from it would usually have little value.

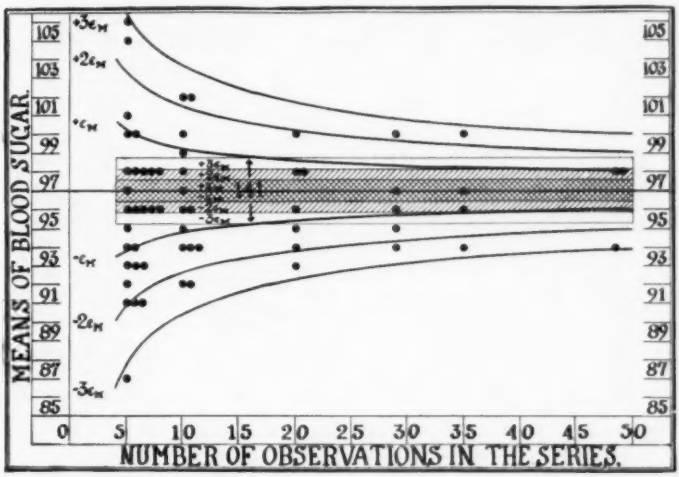

Chart 2.—Distribution of the means of the various component series of the series of 141. The parabolic lines represent in order $\pm$ 1, 2, and 3 times ϵ_M for the series of the indicated number of observations. ϵ_M was calculated from ϵ for the entire series of 141. The dots represent the means of the component series, the heavy horizontal line that for the grand series. The lighter horizontal lines indicate, in order, $\pm$ 1, 2 and 3ϵ for the grand series.

From chart 2 may be read directly the range within which the means of all future series containing five or more observations would be expected to fall, provided that the material and technic were comparable with those we have described.

We were able to make the material still more homogeneous by selecting from the grand series of 141, 120 subjects between the ages of 20 and 25 years, inclusive. In this group the

mean age was 22 ± 1.4 years; the mean weight was 68 ± 9.7 Kg. (113 observations) and the mean blood sugar was 96 ± 7.3 mg. per hundred cubic centimeters.

Hence it appears that the few persons in the grand series who were out-

side of these limits did not materially influence the results. What would have happened had their numbers been greater we are not in a position to say.

A graphic comparison of our series with some of those already in the literature is presented in chart 3. The observations are grouped in classes of 3 mg. and are plotted on the midvalue of the respective class. Similar observations, then, fall on a line, so that the horizontal distances measure class frequencies while vertical distances measure the amount of sugar found. In chart 4, frequency curves are presented showing the distribution of our observations and its relation to the theoretical distribution curve plotted from the mean and mean deviation of the series of 141. On the same coordinates is also plotted a frequency

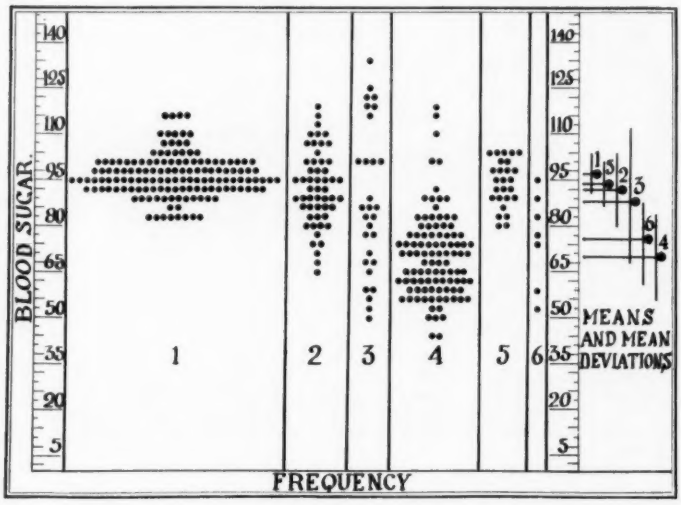

Chart 3.—A graphic comparison of various series of blood sugar determinations on man. Each dot represents an observation. The means and mean deviations are plotted at the extreme right of the chart. *1* indicates the 141 observations reported in this paper; *2*, fifty-three observations of Goto and Kuno, 1921; *3*, twenty-nine observations of Gettler and Baker, 1916, and *4*, 100 observations of Cummins and Piness, 1917. The somewhat low mean of this group is possibly related to the effects of hospitalization since the observations were made on convalescent patients. *5* indicates twenty-six observations of Okey and Robb, 1925. While many more than twenty-six observations were reported in these papers, there were but twenty-six subjects, and to make their work comparable with ours only the initial observations are included. *6* indicates seven observations of Strouse, 1920. Here again many more than seven observations were reported, but for one reason or another only seven could be considered comparable with the other groups.

curve constructed from the data assembled by Gray (1923), which he felt included all trustworthy determinations of normal blood sugar on man up to the time of his publication.

The satisfactory precision of our series on man as compared with that found for rabbits (Eadie,[7] 1923; Scott and Ford,[8] 1923; Clough, Allen and Root,[9] 1923; Scott, 1927) we attribute to the greater uniformity of the human material and of the conditions which preceded the taking of the sample. It could not have been in the analytic technic, since a research on the normal blood sugar of rabbits conducted by one

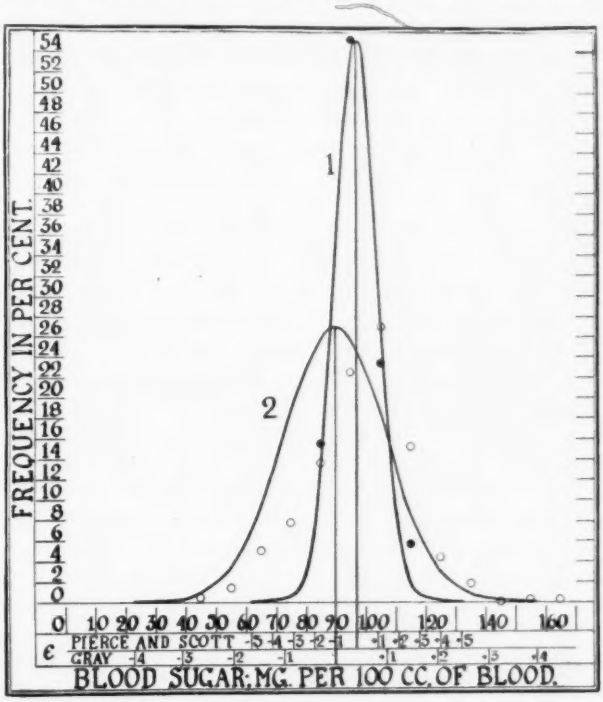

Chart 4.—Frequency curves for human blood sugar. Curve 1 is for the series of 141 observations reported in this paper. Curve 2 is for a series of 431 observations collected by Gray, 1923, from various sources. The frequency is plotted in percentage of the total number of observations in the respective series. The lines are the theoretical curves. The dots and circles show the position of the various classes. The dots indicating series 1 and the circles, series 2. Class interval 10; class limits 0 and 9; positions are plotted on midvalues of the respective classes.

7. Eadie, G. S.: Am. J. Physiol. **63**:513, 1923.

8. Scott, E. L., and Ford, T. H.: Am. J. Physiol. **63**:520, 1923.

9. Clough, H. D.; Allen, R. S., and Root, E. W.: Am. J. Physiol. **66**:461, 1923.

of us (E. L. S., so far unpublished) concurrently with this work, employing the same analyst and methods, yielded a mean deviation essentially the same as previously reported for rabbits and about twice that found by us for man.

In research work, several methods of establishing the necessary norm are available:

1. The norm may be established on one set of subjects, and the experimental conditions imposed on a second, presumably similar, set.

2. The norm may be established on one set of subjects, and at a later date the same subjects may be exposed to the experimental conditions.

3. The norm may be established on a set of subjects, and the experimental conditions may be imposed immediately on the same subjects.

According to the nature of the research: (1) A single observation may be made on each of many subjects; (2) many observations may be made on a single subject, and (3) several observations may be made on each of several subjects.

Examples of each of these practices may be found in the literature, and the question arises as to which of the methods will yield results of the greatest precision and of the most value in making general predictions. The present research is not sufficiently broad to exemplify all of the foregoing possibilities listed, but it does permit of estimation of certain phases, and, where necessary, will be amplified by data selected from the work of Okey and Robb (1925).

Three or more samples of blood were drawn from each of twenty-five persons of our group of 141 subjects, at intervals of not less than a week. The results of the first three determinations on each of these subjects are shown in table 5. It appears that in spite of the day to day variations which obtain for any given person, the means of the three series of twenty-five are remarkably alike; in this case, they are actually identical. That this similarity is not altogether chance is indicated by table 6, which presents five similar series taken from the work of Okey and Robb. Here, while the means are not all identical, they are so nearly alike that their differences may be considered of no physiologic significance. Thus, so far as generalization based on these series is warranted, the mean basal blood sugar level of a group containing a considerable number of persons may be considered as constant. From table 6, it appears that a group of five is not large enough to give this constant value, while a group of twenty-three is satisfactory. The data are not sufficient to permit determination of the minimum number required for a significant series. Nor can we venture prediction as to the time which may be allowed to elapse between the control and the experimental observations on a given group of persons, although the work indicates that this interval may be at least two weeks. It therefore

follows that the experimental work need not immediately succeed the determination of the norm.

Comparison of the series of similar length in table 2 with those of tables 5 and 6 indicates that greater precision may be expected when the same group of persons is used both for the control and for the experiment than when different groups of subjects are employed. It would

TABLE 6.—*Data on Five Consecutive Samples of Blood Taken from Each of Twenty-Three Subjects (from Okey and Robb)* *

	Observation						
	1	2	3	4	5	M	ϵ
1	88	92	93	92	95	92	2.6
2	86	92	102	101	100	96	6.6
3	91	93	95	94	97	94	2.2
4	91	91	91	98	89	92	3.5
5	104	92	87	93	93	94	6.2
M	92	92	94	96	94		
ϵ	6.7	0.2	5.6	3.8	6.2	for 1st 5	
6	93	102	98	91	89	94	4.6
7	100	102	104	105	94	101	4.4
8	91	104	100	105	96	98	5.2
9	90	102	92	106	104	98	7.4
10	84	94	93	80	89	88	6.0
M	92	101	97	96	94		
ϵ	6.7	3.9	5.0	11.2	6.2	for 2d 5	
11	107	95	99	98	101	100	4.5
12	96	97	90	96	97	95	3.0
13	89	84	91	92	85	88	3.6
14	79	92	90	85	87	86	5.1
15	98	103	96	84	84	93	8.8
M	94	94	94	91	90		
ϵ	10.5	7.0	4.5	6.3	7.8	for 3d 5	
16	98	94	92	91	94	94	2.7
17	96	89	91	96	90	92	3.4
18	103	93	87	102	100	97	6.8
19	95	97	93	89	96	94	3.2
20	98	99	102	99	103	100	2.2
M	98	94	93	95	96		
ϵ	6.3	3.9	5.5	6.7	5.1	for 4th 5	
21	103	98	89	87	89	93	7.0
22	92	103	107	94	105	100	6.8
23	91	89	94	93	99	93	3.8
Grand M	94	95	94	94	94		
" ϵ	6.8	5.2	5.5	6.7	6.0		

* In columns 1 to 5 the data appear in their natural order; in columns M and ϵ the means and mean deviations of the five observations on each individual are given. The series of twenty three were also broken up into component series of five observations each. The means and mean deviations of these component series appear in the appropriate rows. Those for the series of twenty-three, respectively, in the next to the last and the last row.

appear, therefore, that though general predictions are as well justified in one case as in the other, within the limits of precision attained, this precision will be greater when the same subjects are used for both determinations.

The mean of the ϵ's for twenty-three series of five observations each on single subjects may be calculated from data found in table 6. The result, 4.4, is to be compared with 5.8, column 6 of table 3, in which the

five observations were made on each of five persons. Similarly, the ϵ_M's are respectively 1.9 and 2.6 and the expirical ϵ_M's, 4 and 4.3. While, as might be expected, these values indicate somewhat less variability when all of the observations are made on one person, the gain in precision is not impressive, and when the loss in the representative character of the series is considered would lead one to avoid this method of procedure when possible. True, this conclusion is based on short series, but there are a considerable number of such series in each group, so that the conclusion is warranted provisionally, and unless the contrary condition is shown to hold, should be a guide in planning a research. The material at hand is not sufficient to yield a large group of longer series based on single persons, but in table 7 are to be found

TABLE 7.—*Seven Series of Ten Observations Each* *

	M, Age 24	C, Age 24		F, Age 31				
	1923	1923	1924	1924	1924	1924	1924	1924
	88	88	109	91	100	100	92	93
	92	92	101	93	96	94	102	89
	93	102	97	95	90	93	93	89
	92	101	99	94	93	94	94	89
	95	100	98	97	88	99	105	—
	81	108	97	91	98	100	101	Total
	85	101	97	91	92	95	97	44 obser-
	100	96	99	98	89	98	89	vations
	90	89	99	99	97	89	94	M, 94
	90	90	98	90	87	90	94	ϵ, 4.3
M	91	97	99	94	93	95	96	
ϵ	5.4	6.8	3.6	3.3	4.5	4.0	5.0	

* All data in a given series are derived from a single subject. Since the data of the last four series are all derived from one subject, together with four additional observations, we are in possession of a similar series of forty-four observations. (From Okey and Robb.)

seven groups of ten observations each made on a single person and one of forty-four observations similarly made. These longer series apparently confirm the conclusion just drawn.

In table 8 are to be found four series of twenty-five observations each, in which five observations were made on each of five persons. A comparison of the ϵ's and of the ϵ_M's of these series with those of group 4, table 2, does not indicate a significant gain in precision over the series in which each observation was made on a different person. On the other hand, such series must have lost a considerable portion of their value as representatives of the general field from which the observations were drawn.

The conclusion seems to be justified that a series attains value as the number of persons on which the observations are made is increased, the ideal series being one in which the number of observations and the number of persons on which they are made are equal.

SUMMARY

1. The blood sugar of young, healthy men and women under basal conditions may vary between values of about 80 and 115 mg. per hundred cubic centimeters of blood. The true mean value probably lies between 95 and 99 mg. per hundred cubic centimeters of blood. This statement presupposes that the determinations are made by the Shaffer-Hartmann or the Folin-Wu method (Duggan and Scott,[4] 1926).

TABLE 8.—*Four Series, Each of Twenty-Five Observations, Five Observations Being Made on Each of Five Subjects (from Okey and Robb)*

	Series			
	1	2	3	4
	88	93	107	98
	92	93	95	94
	93	98	99	92
	92	91	98	91
	95	89	101	94
	88	100	96	96
	92	102	97	89
	102	104	90	91
	101	105	96	96
	100	94	97	99
	91	91	89	103
	93	104	84	93
	95	100	91	87
	94	102	92	102
	97	96	85	100
	91	90	79	95
	91	102	103	97
	91	92	90	93
	98	106	85	89
	89	104	87	96
	104	84	98	98
	92	94	103	99
	87	93	98	102
	93	80	84	99
	93	89	84	103
M	94	96	93	95
ϵ	4.4	6.9	7.3	4.7
ϵ_M	0.9	1.4	1.5	0.9

2. The probability is about 95 per cent that the mean of any such series consisting of twenty-five or more observations made on as many persons will not differ more than three times its mean deviation from this true mean.

3. Conclusions based on series containing fewer than twenty-five observations are of doubtful significance when the observations pertain to the blood sugar of man. When greater absolute precision is required to support the conclusions than is indicated by $3\,\epsilon_M$ for twenty-five terms, a longer series must be obtained.

4. From this it follows that within these limits the mean value of a series of twenty-five or more blood sugar determinations, each of which is made on a different person, may be considered as a constant. Evidence is presented to substantiate this conclusion.

5. A series of observations gains in general significance as the number of subjects on which the observations are made increases; the slightly greater percision which is attained by making many observations on a single person is more than offset by the loss in the representative character of the series.

BACTERIOLOGIC EXAMINATION OF SEVEN HUNDRED AND TWENTY-FOUR SPUTUMS FROM AS MANY PATIENTS WITH BRONCHIAL ASTHMA*

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During the past ten years we have been interested in the bacteriology of the nonsensitive or asthmatic bronchitis type of asthma, since it is in this type that less is known concerning the cause; furthermore, this type seems to be infectious. Specimens of sputum from 724 patients have been studied during this time. It is during the changeable and cold seasons of the year that the majority of patients suffer from asthmatic bronchitis; therefore, the bacteriologic examinations have been made during the fall, winter and spring of each year since 1918. Consequently, this study was divided into nine periods, namely, the fall, winter and spring of each year since 1918.

Previous to this study, we were accustomed to classify streptococci into three groups, namely, *Streptococcus viridans*, *S. hemolysans* and *S. alpha hemolysans*, but it was soon learned that this classification was not only confusing, but incomplete. It was confusing because the same organism on the same plate would sometimes produce a wide area of hemolysis about several colonies and a narrow area of hemolysis about other colonies; therefore, instead of having two types of organisms, *hemolysans* and *alpha hemolysans*, we had one type of organism producing two grades of hemolysis. The old classification is incomplete in that frequently types of colonies were encountered that produced a brownish pigment or no pigment; therefore, since these colonies were not hemolytic and did not produce a green pigment such as *viridans*, they were not accounted for in the old grouping. Since all types of streptococci either do or do not produce hemolysis, and it is rarely difficult to determine whether there is or is not hemolysis about a colony, we adopted for this work the classification of hemolytic and nonhemolytic streptococci. All colonies were considered as either hemolytic or nonhemolytic, but for completeness the various types of colonies were noted.

Each of these two main groups of streptococci, hemolytic and nonhemolytic, were further subdivided according to Holman's [1] classification

* From the Laboratory of the Medical Clinic of the Peter Bent Brigham Hospital.

1. Holman, W. L.: The Classification of Streptococci, J. M. Research **34**:377, 1916.

into eight subgroups according to their ability to ferment the carbohydrates, salicin, mannite and lactose, in times serum waters made according to the method of Hiss.[2]

TECHNIC

Throughout this work the following bacteriologic technic was used: Thick masses of sputum, which was raised during an asthmatic attack or during a severe paroxysm of coughing which usually occurred in the morning, were washed in sterile sodium chloride solution and shaken in 5 cc. of plain bouillon. Tubes of melted plain agar to which 0.5 cc. of sterile defibrinated human blood was added were inoculated with varying amounts of the plain bouillon emulsion of sputum, poured into Petri dishes and incubated for thirty-six hours. Various types of colonies were then picked off, subcultivated in dextrose bouillon, and

TABLE 1.—*Prevalence and Frequency of Hemolytic and Nonhemolytic Streptococci and of Other Organisms*

Number of	1918-1919	1919-1920	1920-1921	1921-1922	1922-1923	1923-1924	1924-1925	1925-1926	1926-1927
Sputums examined	65	65	56	80	65	101	93	95	104
Hemolytic varieties recovered	51	46	49	70	68	21	54	42	110
Hemolytic varieties predominated	35	16	4	6	5	2	8	6	21
Hemolytic varieties alone	1	1	27	12	43	6	5	7	14
Nonhemolytic varieties recovered	54	51	24	62	26	108	115	93	115
Nonhemolytic varieties predominated	24	28	2	3	1	2	7	5	30
Nonhemolytic varieties alone	1	13	19	14	11	82	48	35	31
Hemolyticus subacidus recovered	17	19	0	8	2	2	8	13	42
Hemolyticus anginosus recovered	13	16	11	29	5	9	18	5	17
Hemolyticus infrequens recovered	8	3	16	12	28	2	10	11	14
Hemolyticus pyogenes recovered	10	7	20	14	26	6	10	4	7
Hemolyticus equinus recovered	1	0	1	2	2	0	2	0	7
Hemolyticus type I recovered	2	1	1	4	4	1	5	6	20
Hemolyticus type II recovered	0	0	0	0	1	0	1	1	1
Hemolyticus type III recovered	0	0	0	1	0	1	0	2	3
Nonhemolyticus ignavus recovered	16	20	0	5	0	13	12	28	45
Nonhemolyticus salivarius recovered	15	19	5	13	2	18	34	9	18
Nonhemolyticus fecalis recovered	3	5	10	19	9	28	25	29	14
Nonhemolyticus mitis recovered	14	7	8	17	10	25	17	4	10
Nonhemolyticus equinus recovered	0	0	0	1	0	6	4	4	5
Nonhemolyticus type I recovered	6	2	1	4	5	12	16	16	17
Nonhemolyticus type II recovered	0	0	0	0	0	4	1	1	3
Nonhemolyticus type III recovered	0	0	0	3	0	1	6	2	3
Strains of staphylococci recovered	8	16	1	5	5	16	8	4	4
Strains of bacilli recovered	6	8	5	7	8	1	10	6	10
Strains of other organisms recovered	5	5	3	0	2	0	0	0	3

incubated for about twenty-four hours. The organisms from this dextrose bouillon growth were stained by Gram's method, and a bile solubility test was made; those organisms which proved to be gram-positive cocci in chains, noncapsulated and bile-insoluble, were inoculated, according to the method of Hiss,[2] into litmus serum waters which contained salicin, mannite and lactose. These serum waters were incubated for fourteen days unless coagulation took place before that time, and at the end of fourteen days, after the tubes in which change had not taken place were carefully examined to make sure that organisms were present, the organisms were named according to Holman's[1] method of classification.

Table 1 shows for each period already defined the prevalence of hemolytic and nonhemolytic streptococci, also the frequency of each of the subgroups of both of these two types of streptococci and the prevalence of organisms other than

2. Hiss, P. H., in Hiss and Zinsser: Textbook of Bacteriology, New York, D. Appleton & Company, 1927.

streptococci. Naturally, when various colonies were picked off from plates, many duplicates were picked off and inoculated into the serum waters. In the table, however, duplicates are not recorded; only one variety of each organism that was recovered from the same sputum is shown. For instance, if two strains of hemolytic *Streptococcus subacidus* were recovered, only one would be recorded; therefore, qualitative rather than quantitative observations are represented.

Following the discussion of the observations as recorded in table 1, a few paragraphs are devoted to the results from changes in the original technic. The different technic will be described at that time. The reason for this change, which was carried on in conjunction with and merely supplemented, the original technic, was to check up on the original technic and either to substantiate or to disprove the observations.

During the season 1918-1919, a specimen of sputum was taken and studied from seventy-five patients suffering from asthma. Fifty-one strains of hemolytic streptococci were recovered from forty-six of these patients; in thirty-five specimens of sputums this type of organism predominated, and in one specimen no other organism was found. These fifty-one strains of hemolytic streptococci were distributed among the following types: *infrequens,* eight strains; *anginosus,* thirteen strains; *pyogenes,* ten strains; *hemolyticus* I, two strains; *subacidus,* seventeen strains, and *equinus,* one strain; no strains of *hemolyticus* II and III were recovered. Fifty-four strains of nonhemolytic streptococci were recovered from thirty-seven of the patients; in twenty-four of the specimens this type predominated, and once it was found alone. These fifty-four strains were distributed as follows: *fecalis,* three strains; *nonhemolyticus* I, six strains; *mitis,* fourteen strains; *salivarius,* fifteen strains, and *ignavus,* sixteen strains; no strains of *nonhemolyticus* II and III or of *equinus* were recovered.

Organisms, other than streptococci, that were recovered from the sixty-five specimens of sputum were as follows: *Staphylococcus pyogenes-aureus,* eight times; *Micrococcus tetragenous,* once; a diphtheroid bacillis, twice; *Bacillus subtilis,* six times, and *Staphylococcus pyogenes-albus,* twice.

To summarize these observations, all but three of the fifty-one strains of hemolytic streptococci were included in the four types, *subacidus, anginosus, pyogenes* and *infrequens.* All but three of the fifty-four strains of nonhemolytic streptococci were included in the four following types, namely: *ignavus, mitis, salivarius* and *nonhemolyticus* I. The different strains of streptococci were practically equally divided between hemolytic and nonhemolytic but in thirty-five specimens of sputum the hemolytic type of colony predominated, whereas in twenty-four specimens the nonhemolytic type predominated. *Staphylococcus pyogenes-aureus* was found eight times and was the only organism other than streptococci that was recovered with any degree of frequency.

During the period 1919-1920, sixty-five specimens of sputum from as many persons were studied and streptococci were recovered from fifty-nine of the specimens. Hemolytic streptococci were found in forty-six specimens; in sixteen the hemolytic type predominated; in one, it was the only organism found. The forty-two strains of hemolytic streptococci were distributed as follows: *infrequens,* three strains; *hemolyticus* I, one strain; *pyogenes,* seven strains; *anginosus,* sixteen strains; *subacidus,* nineteen strains; no strains of *hemolyticus II* and III or of *equinus* were recovered.

Nonhemolytic streptococci were recovered from fifty-one specimens; in twenty-eight this type of streptococcus predominated; in thirteen, it was the only organism recovered. The fifty-one strains were grouped as follows: *fecalis,* five strains; *nonhemolyticus* I, two strains; *mitis,* seven strains; *salivarius,* nineteen strains; *ignavus,* twenty strains; no strains of *nonhemolyticus* II and III or of *equinus* were recovered.

Organisms other than streptococci that were recovered from the sixty-five specimens were: *Staphylococcus pyogenes-aureus,* sixteen times; *S. pyogenes-albus,* three times; a gram-negative bacillus, eight times; *Micrococcus tetragenous* and *Bacillus subtilis,* one time each.

The observations during this period may be summarized as follows: The nonhemolytic streptococci outnumbered the hemolytic in the proportion of fifty-one of the former to forty-six of the latter; the former predominated in twenty-eight specimens of sputum against the latter in sixteen; and in thirteen specimens the nonhemolytic type was the only organism found, whereas in only one specimen was the hemolytic type found alone. Of the forty-six strains of hemolytic streptococci, all but one were included in the following four types: *infrequens, pyogenes, anginosus* and *subacidus.* Of the fifty-one strains of nonhemolytic streptococci, all but two were included in the following four types: *mitis, ignavus, salivarius* and *fecalis.* The only organisms other than streptococci that occurred with any frequency were *Staphylococcus pyogenes-aureus,* sixteen times, and a gram-negative bacillus, eight times.

During the period 1920-1921, fifty-six specimens of sputum were plated. A total of forty-nine strains of hemolytic streptococci were recovered; in twenty-seven specimens, this type of organism was the only one recovered, and in four other specimens it predominated. The forty-nine strains of hemolytic streptococci were divided among the following types: *anginosus,* eleven; *infrequens,* sixteen; *pyogenes,* twenty; *equinus,* one; *hemolyticus* I, one; strains of *subacidus* or of *hemolyticus* II or III were not recovered.

Only twenty-two strains of nonhemolytic streptococci were recovered; in nineteen specimens of sputum it was the only organism recovered and in two other specimens it predominated. The nonhemolytic

streptococci were of the following types: *salivarius,* five; *fecalis,* ten; *mitis,* eight; *nonhemolyticus* I, one; no strains of *ignavus, equinus* or of *nonhemolyticus* II or III were recovered.

The outstanding differences between the results of this period and those of the two former periods which were similar were that twice as many hemolytic types were recovered as nonhemolytic. In about one half of the sputums, hemolytic streptococci were the only organisms found, and in nearly as many specimens, the nonhemolytic type was the only organism recovered; in other words, most of the specimens of sputums grew either type of organism alone, and in only a few were both types found. Another distinct difference was the absence of *hemolyticus subacidus* and *nonhemolyticus ignavus;* both of these organisms were more prevalent than any of the other types in the previous two periods. Other differences were the large proportion of *infrequens, pyogenes* and *fecalis,* the decreased frequency of *salivarius* and the fact that staphylococci were recovered only once.

During the period of 1921-1922, eighty specimens of sputum were examined. Seventy strains of hemolytic streptococci were recovered; in twelve specimens of sputum, it was found alone and in six other specimens it predominated. These hemolytic streptococci were of the following types: *subacidus,* eight strains; *anginosus,* twenty-nine strains; *infrequens,* twelve strains; *pyogenes,* fourteen strains; *equinus,* two strains; *hemolyticus* I, four strains, and *hemolyticus* III, one strain.

Sixty-two strains of nonhemolytic streptococci were recovered. In fourteen sputums examined it was found alone and in three other specimens it predominated. These nonhemolytic streptococci fell into the following groups: *ignavus,* five; *salivarius,* thirteen; *fecalis,* nineteen; *mitis,* seventeen; *equinus,* one; *nonhemolyticus* I and III, four and three, respectively.

The chief differences to be noted in this period were the large numbers of both hemolytic and nonhemolytic organisms recovered; in two thirds of the sputum examined both types of organisms were present in about equal numbers. The types *anginosus* and *fecalis* were present in unusually large numbers; *mitis* was more prevalent than formerly, and in proportion *subacidus* and *ignavus* were recovered less frequently.

During the season 1922-1923, sixty-five specimens of sputum were plated. From these, sixty-eight strains of hemolytic streptococci were recovered; in forty of these specimens examined it was the only organism recovered, and in five others it predominated. The sixty-eight strains were divided among the following: *subacidus,* two; *anginosus,* five; *infrequens,* twenty-eight; *pyogenes,* twenty-six; *equinus,* two; *hemolyticus* I, four, and *hemolyticus* II, one.

Only twenty-six strains of nonhemolytic streptococci were recovered; in one specimen of sputum, this organism predominated and in eleven other specimens it was the only organism recovered. The twenty-six strains of nonhemolytic streptococci were as follows: *salivarius,* two; *fecalis,* nine; *mitis,* ten; *nonhemolyticus* I, five.

Therefore, during this season the hemolytic streptococci greatly outnumbered the nonhemolytic streptococci. Of the hemolytic streptococci, all but fourteen strains were either *infrequens* or *pyogenes,* both of which were practically equal in numbers, and together they totaled fifty-six strains. Of the nonhemolytic strains, all but seven were either *fecalis* or *mitis,* and there were nine strains of the former and ten of the latter.

During the season 1923-1924, 101 specimens of sputum were plated. From this large number, only twenty-one strains of hemolytic streptococci were recovered; in two specimens this type of organism predominated and in six others, it was the only organism recovered. These twenty-one strains of hemolytic streptococci were divided among the following types: *subacidus,* two; *anginosus,* nine; *infrequens,* two; *pyogenes,* six; *hemolyticus* I and III, one each.

One hundred and eight strains of nonhemolytic streptococci were recovered; in two specimens of sputum this type of organism predominated, and in eighty-two it was the only organism present. The 108 strains of nonhemolytic streptococci were classified as follows: *ignavus,* thirteen strains; *salivarius,* eighteen; *fecalis,* twenty-eight; *mitis,* twenty-five; *equinus,* five; *nonhemolyticus* I, twelve; II, four, and III, one.

The results of this period were different from those of former seasons. There was a great scarcity of hemolytic streptococci and as great a preponderance of nonhemolytic streptococci. Among the few hemolytic strains, *anginosus,* which was recovered nine times, occurred most frequently and *pyogenes,* isolated six times, was next in frequency; no other hemolytic strains occurred more often than twice. All eight varieties of nonhemolytic streptococci were recovered for the first time, and the following five varieties were recovered often enough to be mentioned as predominating: *ignavus, salivarius, fecalis, mitis* and *nonhemolyticus* I; the latter had not been recovered with any degree of frequency in former periods. *Staphylococcus pyogenes-aureus* was also recovered with the usual frequency.

During the season 1924-1925, ninety-three specimens of sputum were plated. A total of fifty-four strains of hemolytic streptococci were recovered; in eight specimens, this type of organism predominated, and in five others it was the only organism recovered. These fifty-four strains of hemolytic streptococci were the following: *subacidus,* eight; *anginosus,* eighteen; *infrequens,* ten; *pyogenes,* ten; *equinus,* two; *hemolyticus* I, five, and II, one.

One hundred and fifteen strains of nonhemolytic streptococci were recovered; in seven specimens this type of organism predominated and in forty-eight it was the only organism recovered. The 115 strains of nonhemolytic streptococci were the following: *ignavus,* twelve strains; *salivarius,* thirty-four; *fecalis,* twenty-five; *mitis,* seventeen; *equinus,* four; *nonhemolyticus* I, sixteen, and II and III one and six, respectively.

In this period, the hemolytic streptococci were recovered in the average frequency of former periods and, as usual, *anginosus, infrequens* and *pyogenes* were most often encountered, and *anginosus* was more prevalent than in some years. Nonhemolytic streptococci, however, were recovered more frequently than in the past, and the same varieties that were most prevalent in the previous period were again most frequently encountered during this period; there were *equinus, salivarius, fecalis, mitis* and *nonhemolyticus* I, and these were recovered a similar number of times as formerly, with the exception of *salivarius* which was recovered twice as frequently as in any former year.

During the season 1925-1926, ninety-five specimens of sputums were examined. From these, forty-two strains of hemolytic streptococci were recovered; in seven specimens, it was the only organism found and in six others it predominated. The following hemolytic strains were recovered: *subacidus,* thirteen; *anginosus,* five; *infrequens,* eleven; *pyogenes,* four; *hemolyticus* I, six; *hemolyticus* II and III, one and two, respectively.

A total of ninety-three strains of nonhemolytic streptococci were recovered; this type of organism predominated in five specimens of sputum, and it was the only organism recovered in thirty-five specimens. The nonhemolytic strains were as follows: *anginosus,* twenty-eight; *salivarius,* nine; *fecalis,* twenty-nine; *mitis,* four; *equinus,* four; *nonhemolyticus,* I, sixteen; *nonhemolyticus* II and III, one and two, respectively.

The observations of this period resembled those of the former period as to the prevalence of both hemolytic and nonhemolytic streptococci in the sputums that were cultured, but the prevalence of the different strains of these two types of streptococci varied as follows: Of the hemolytic strains, *subacidus* was more prevalent and *anginosus* and *pyogenes* were distinctly less prevalent than usual. Among the nonhemolytic types, *ignavus* was more prevalent than usual, and *mitis* and *salivarius* were much less prevalent than usual. During this period, the majority of the hemolytic strains were *subacidus* and *infrequens* and the majority of the nonhemolytic strains were *ignavus, fecalis* and *nonhemolyticus* I.

During the season 1926-1927, 104 specimens of sputum were plated. One hundred and ten strains of hemolytic streptococci were recovered;

it was the only organism found in fourteen of the specimens examined, and it predominated in twenty-one. These hemolytic strains were the following: *subacidus,* forty-two; *anginosus,* seventeen; *infrequens,* fourteen; *pyogenes,* seven; *equinus,* seven; *hemolyticus* I, twenty; *hemolyticus* II and III, two and three, respectively.

One hundred and fifteen strains of nonhemolytic streptococci were recovered; in thirty specimens of sputum this organism predominated and in thirty-one other specimens it was the only organism recovered. These nonhemolytic strains were the following: *ignavus,* forty-five; *salivarius,* eighteen; *fecalis,* fourteen; *mitis,* ten; *equinus,* five; *nonhemolyticus* I, seventeen, and *nonhemolyticus* II and III, three each.

During this period, hemolytic streptococci were recovered more frequently than formerly, and nonhemolytic streptococci were recovered with about the same frequency as during the past four periods. Of the hemolytic strains, *subacidus, hemolyticus* I and *equinus* were more frequent than formerly, *pyogenes* was recovered less frequently; *anginosus* and *infrequens* were found with the usual frequency. Among the nonhemolytic streptococci, *ignavus* was much more prevalent than formerly and *mitis* was less prevalent than usual; *salivarius, fecalis* and *nonhemolyticus* I were recovered in nearly the same numbers as usual. Another unusual observation this season was that more varieties than usual were prevalent in large numbers, and the nonhemolytic included five varieties, whereas formerly two or three varieties usually comprised the greater number of organisms.

In table 1, the variation in the occurrence of the different varieties of streptococci that were prevalent during the different periods is evident. It is not shown, however, whether there is any variation during each period. A careful study of each period does not reveal any distinct variation for that period; in other words, practically the same varieties of streptococci that were prevalent during the fall months continued to be similarly prevalent during the succeeding winter and spring months. Therefore, whatever variation occurred during the periods studied was brought about by the intervening summer months. In other words, the same varieties of streptococci prevailed throughout the successive cool months of each year, but the intervening warm summer period often altered considerably the prevailing streptococci so that in the next successive fall, winter and spring different varieties of streptococci from those of the preceding fall, winter and spring prevailed.

Another point not brought out in the table, but which may be of interest, is a discussion regarding the number of different varieties of streptococci that were recovered from the same sputum. In 43 per cent of the specimens of sputum examined, only one variety of streptococcus was recovered; in 34 per cent, two different varieties were recovered; in

16 per cent, three different varieties were found; in 4 per cent, four varieties and in 1 per cent, five varieties were recovered. Therefore, from a third of the specimens only two different varieties of streptococci were recovered and from less than a third of the specimens more than two different varieties. When more than one different strain of streptococcus was recovered from the same sputum, all strains were sometimes of the hemolytic type, sometimes of the nonhemolytic type; often both types were represented. In other words, one specimen might contain any combination of the sixteen different varieties of streptococci, although usually a total of five different varieties was not exceeded, but in a third of the sputums examined there was a combination of only two different varieties, and in less than a third of the specimens the combination consisted of more than two different varieties.

VARIATIONS IN TECHNIC

During the periods of 1918-1919 and 1919-1920, in addition to the technic already described, the majority of the organisms were carried through further subcultures. The organisms from the dextrose bouillon growth which was cultured from individual colonies on blood agar plates were again plated on blood agar and grown for twenty-four hours. From these second plates, different colonies were again fished and inoculated into dextrose bouillon and incubated for twenty-four hours. From these bouillon cultures, the litmus serum waters containing the three carbohydrates were inoculated as previously described. This second plating made it certain that the organism which was inoculated into serum waters was in pure culture, whereas only one plating, the usual number throughout this work, might leave one in doubt as to the purity of the organisms that were inoculated into the carbohydrate serum waters.

The results as judged by the serum water fermentation tests were identical with both methods for all of those organisms that survived the second plating; therefore, it is fair to assume that one plating resulted either in a pure culture, or, if not, the contamination was too slight to influence the fermentation test. At any rate, one plating when done with care is satisfactory. It was found that the second plating was unsatisfactory, because so many organisms that were hemolytic in the first place either failed to grow or lost their hemolytic property in the second plate.

During the season 1920-1921, it was noted that from the first twenty-five specimens of sputum plated nearly always only one type of streptococcus, either hemolytic or nonhemolytic, was recovered, and that it was rare to recover both types from the same sputum. This was different from the results of the two former seasons and was rather disturbing. Therefore, in addition to the usual method of plating, the

following technic was used, so that two different specimens of the same sputum were plated. Some of the washed sputum was grown in dextrose bouillon over night, and from this culture blood agar plates were inoculated and incubated for thirty-six hours. From these plates various colonies were picked, macerated in small quantities of dextrose bouillon and then inoculated into the Hiss litmus serum water containing the three carbohydrates. Thirty specimens were cultured in this manner, and in twenty-seven the results, as judged by the fermentation of the serum waters, were identical for both methods of plating; the same forty-two strains of the various types were identical for both methods. In three specimens, there were the following differences: in one sputum, only *pyogenes* was recovered by the original method, whereas both *pyogenes* and *anginosus* were recovered by the second method; in another sputum, *pyogenes* and *subacidus* were recovered by the original method but only *pyogenes* by the second method; in the third sputum, *pyogenes* and *infrequens* were recovered by the original method, but in addition to these, *mitis* was also recovered by the second method. Therefore, in these three specimens there were identical observations with four strains and different observations with three strains. Since in the forty-nine strains recovered from the thirty specimens there were only three variations, and in the thirty sputums there was only one material change, namely, one was changed from purely hemolytic to both hemolytic and nonhemolytic, it is evident that the observations already reported as made by the original method of plating must be accurate for practical purposes.

During the study, duplicates of colonies with similar morphologic characteristics were picked off and inoculated into dextrose bouillon and then into the serum waters, but frequently, since all colonies proved to contain the same organism, only one variety of either the hemolytic or nonhemolytic type was recovered. Since, as already described, the method of plating was not at fault, it was felt that possibly an insufficient number of colonies were being picked from the original plates with the result that some strains were being missed. Therefore, beginning in the period 1922-1923, and continuing throughout the remaining periods, many more colonies were picked from the plates. Several colonies of each of those having different morphologic characteristics were picked off; the phrase "different morphologic characteristics of the colonies" will be discussed later. By picking off these colonies, however, it was learned that rarely was a variety of organism missed when fewer colonies were picked off, and when a large number of colonies were picked off, only a larger number of duplicates were obtained. For example, if a plate contained only colonies of nonhemolytic streptococci, when two dark green colonies were picked off and cultured in the carbohydrate serum waters, both turned out to be *salivarius;* when four colonies were

similarly selected, all four would be the same. For another example, two colonies of a narrow hemolytic and two of a wide hemolytic character might be selected. The two narrow hemolytic colonies might be, for example, *pyogenes,* and the two wide hemolytic colonies might be, for instance, *subacidus.* When four of the narrow and four of the wide hemolytic colonies were selected, the result would be the same, namely, four strains of *pyogenes* and four of *subacidus.* If great care is exercised in determining the morphologic characteristics of the colonies and duplicate colonies of each different type are picked off, there is only a slight chance of missing some variety of streptococcus.

Early in the period 1923-1924, it was noted that few hemolytic colonies and a great preponderance of nonhemolytic colonies were being obtained; also that the nonhemolytic colonies were much out of the usual proportion. As it was thought that possibly thirty-six hours was not a sufficient time to allow some colonies to produce hemolysis, a duplicate plate was permitted to incubate for forty-eight hours and sometimes longer, but this added length of incubation did not increase the number of hemolytic colonies, nor did any nonhemolytic colonies become hemolytic. Therefore, there was a real preponderance of nonhemolytic streptococci. It might be well to state at this point that incubation of plates for only twenty-four hours is liable to result in the missing of hemolytic colonies; that is, some colonies that are minute and do not show hemolysis after twenty or twenty-four hours' growth will by thirty-six hours become larger and show definite hemolysis.

MORPHOLOGY

During this work, four distinct types of hemolytic colony of streptococci were evident. They were: a pinpoint colorless colony surrounded by a narrow zone of hemolysis; a pinhead colony, sometimes white, sometimes brownish, surrounded by a zone of hemolysis about as broad as the diameter of the colony; a pinpoint or pinhead colony surrounded by a wide zone of hemolysis, and a green colony surrounded by a narrow zone of hemolysis. The latter type of colony was not observed frequently, but the three former types were usual. The various strains of hemolytic streptococci, however, did not show strict adherence to any one type of colony; in fact, the type of colony for the different strains varied among the three usually described to such a degree that no inference could be drawn from the appearance of the colony as to the type of organism it contained. In the same plate, for example, *subacidus* would produce both a wide and a narrow zone of hemolysis and the size of the colonies would be both pinpoint and pinhead. Although usually the large colonies showed the wide zone of hemolysis, in the same plate a small colony with a wide zone of hemolysis and a large colony with a narrow

zone of hemolysis would be noted. Therefore, the importance of picking off all of the different types of colonies for study is evident, although in so doing several duplicates of the same organism will result, and, as already shown, more than three different varieties of streptococci in the same specimen of sputum is unusual; the usual number is only one or two different varieties.

Three types of nonhemolytic streptococci were noted. A green colony was most frequently encountered, a brown colony was almost as frequently noted, and a white colony was occasionally noted. All of the eight varieties of nonhemolytic streptococci, however, developed into any of these three types of colony and not infrequently the same type of organism would produce two types of colony on the same plate. Therefore, the pigment of the nonhemolytic colony, as Holman [1] found, cannot be taken as a criterion of the strain of the streptococcus present.

The morphology of the organisms themselves also varied. The same organism might be present from one colony as a long chain and from another in a short chain on the same plate. The same organism would be large cocci in chains in one colony and small diplococci in chains in another colony, both colonies being from the same plate. For example, from the same plate *anginosus* was described in the two following ways: wide hemolysis containing long chains of large cocci and narrow hemolysis containing short chains of diplococci. The length of the chain and the size of the individual coccus were not criterions as to the type of the organism.

CONCLUSIONS

From the bacteriologic examination of 724 washed specimens of sputum from the bronchial tubes of as many patients with asthmatic bronchitis the following facts are evident:

The prevalence of hemolytic and nonhemolytic streptococci varies from year to year, but it does not seem to vary during the cool period of the same year; changes in prevalence occur during the summer season.

The presence of the subgroups or individual varieties of both hemolytic and nonhemolytic streptococci varies in the same manner. One year a certain organism may not be present at all (*ignavus*, 1922-1923), and another year it may represent nearly half of all the strains of that particular type (*ignavus* 1926-1927). Such wide variations are, however, unusual.

Among the hemolytic varieties of streptococci, not more than four of the eight were predominant during any one period, and among the nonhemolytic varieties of streptococci, not more than five of the eight predominated during any one period; usually a lesser number of varieties were predominant.

In any one specimen of sputum, it was unusual to recover more than three different varieties of streptococci; in one third of the specimens, only two varieties were recovered, and in more than one third of the specimens, only one variety of streptococcus was recovered.

The morphology of the colony or of the organism is not a criterion as to the particular organism; litmus serum waters containing salicin, mannite and lactose (Holman's method) separate the individual organism.

With the exception of *Staphylococcus pyogenes-aureus*, which occasionally is present in notable numbers, bacteria other than streptococci are not prevalent in the sputum of asthmatic patients in sufficient numbers to be comparable to the streptococcus group.

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Book Reviews

ENDOKRINE KRANKHEITEN. VON PROF. DR. HANS CURSCHMANN, Direktor der Medizinischen Universitätsklinik zu Rostock I. M. Mit einem Beitrag von Dr. Med. et Phil. Franz Prange, M.D., Assistent der Medizinischen Universitatsklinik zu Rostock I. M. Paper. Price, 8.50 marks. Pp. 151, with 48 illustrations and index. Leipzig: Theodor Steinkopff, 1927.

Dr. Curschmann has written the chapters on the thyroid, parathyroid, the hypophysis and the suprarenals, and Dr. Prange has written the chapter or section on diseases of the ovaries and testis. The authors succeeded best in the description and classification of the syndromes related to hyperactivity and hypoactivity on the various endocrine glands. They were more unfortunate in the theoretical part of the work. There is a brief introduction of less than five pages which contains an amazing assortment of dogmatic assertions, theories and questionable facts, as shown by the following quotations:

"It seems to be established that none of the hormones partake of the chemical nature of proteins." We have rather clear evidence that the thyroid hormone as it leaves the thyroid gland is a protein or at least in combination with the protein thyroglobulin.

The following statement is certainly questionable: "Disturbances due to malfunction of single endocrine glands (monoglandular disturbances) are never seen; all endocrine disturbances are of pluriglandular origin." The author states further that "hormones act on the entire metabolism, on the nervous system, and especially on the vegetative nervous system."

"We know that hormones act especially on the sympathetic and parasympathetic systers." "There is no question that the entire endocrine system is under the control of the central nervous system (zerebralen Zentren)."

The author compares this cerebral center (hypothetically located in the mesencephalon) to the keyboard of a piano. It need not be pointed out that this conception of the delicate control of all the endocrine glands through cerebral activity is entirely hypothetic, and yet the author states it as a proved fact.

The thymus gland is included, without question, among the endocrines, although the evidence for such function on the part of this gland is questionable. And, finally, the author classes choline as the hormone of gastro-intestinal motility, a theory which is questionable.

In the sections dealing with the specific endocrine malfunctions when the authors are closer to their own practical experience, they display more evident respect for facts and more critical judgment. Nevertheless, we find such statements as the following, speaking of spasmophilia in children: "There is no doubt that hypofunction of the parathyroids plays a rôle in infantile convulsions or spasmophilia."

Such ex cathedra teaching does not establish the facts and hinders rather than helps the solution of the problem. There is no chapter on the pancreas, insulin and diabetes. The illustrations in the book are on the whole well chosen and classic, but the monograph as a whole cannot be considered a significant contribution to medical science or to medical practice.